

Sequence Summary of HuCAL-Fab1 Library

VL

Framework 1																				CDR 1										Framework 2										CDR 2																														
1										2										3										4										5																														
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9																					
	EcoRV										BstXI										PstI										KpnI										SseXI										AseI										SmaI									
VLx1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	G	I	S	-	-	-	S	Y	L	A	W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q	S	G	V	P								
VLx2	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	L	H	S	-	-	N	G	Y	N	Y	L	D	W	Y	L	Q	K	P	G	Q	S	P	Q	L	L	I	Y	L	G	S	N	R	A	S	G	V	P				
VLx3	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	V	S	-	-	-	S	Y	L	A	W	Y	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	G	A	S	S	R	A	T	G	V	P								
VLx4	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R	A	T	I	N	C	R	S	S	Q	S	V	L	Y	S	S	N	K	N	Y	L	A	W	Y	Q	Q	K	P	G	Q	P	P	K	L	L	I	Y	W	A	S	T	R	E	S	G	V	P						
VLx1	D	I	V	L	T	Q	P	P	-	S	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	S	N	I	G	S	-	-	-	N	Y	V	S	W	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	D	N	Q	R	P	S	G	V	P							
VLx2	D	I	A	L	T	Q	P	A	-	S	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	S	D	V	G	G	Y	-	-	N	Y	V	S	W	Y	Q	Q	H	P	G	K	A	P	K	L	M	I	Y	D	V	S	N	R	P	S	G	V	S						
VLx3	D	I	E	L	T	Q	P	P	-	S	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	L	G	D	-	-	-	-	K	Y	A	S	W	Y	Q	Q	K	P	G	Q	A	P	V	L	V	I	Y	D	D	S	D	R	P	S	G	I	P							
EnvOv											BstXI										SseXI										KpnI										XmaI										BstI										Bst36I									

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Fig. 1a

VH

Framework 1																				CDR 1										Framework 2										CDR 2																									
1										2										3										4										5										6															
M1el																				BspEI																				BspXI										XhoI															
1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0																
VH1A	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	G	T	F	S	S	-	-	Y	A	I	S	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	I	L	P	-	-	I	F	G	T	A	N	Y	A	
VH1B	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	I	N	P	-	-	N	S	G	G	T	N	Y	A	
VH2	Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	C	T	F	S	G	F	S	L	S	T	S	G	V	G	V	G	W	I	R	Q	P	P	G	K	A	L	E	W	L	A	L	I	D	-	-	-	W	D	D	K	Y	Y	S			
VH3	Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	S	-	-	Y	A	M	S	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	A	I	S	G	-	-	S	G	G	S	T	Y	Y	A	
VH4	Q	V	Q	L	V	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	G	S	G	G	S	T	S	-	-	Y	Y	W	S	W	I	R	Q	P	P	G	K	G	L	E	W	I	G	I	Y	-	-	Y	S	G	S	T	N	Y	N			
VH5	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	Y	S	F	T	S	-	-	Y	W	I	G	W	V	R	Q	M	P	G	K	G	L	E	W	M	G	I	I	V	P	-	-	G	D	S	D	T	R	Y	S
VH6	Q	V	Q	L	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	W	I	R	Q	S	P	G	R	G	L	E	W	L	G	R	T	Y	Y	R	-	-	S	K	W	Y	N	D	Y	A	

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Fig. 1a cont.

Framework 3										CDR 3										Framework 4									

Fig. 1b

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Sequence Summary of HuCAL-Fab1 Library

VL

Framework 1																			
CDR 1																			
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
VLx1	GAT	ATC	CAG	ATG	ACC	CAG	AGC	CAG	GGT	GAT	CGT	GTG	ACC	ATT	AGC	AGC	—	—	—
VLx2	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CAG	GGT	GAT	CGT	GTG	ACC	ATT	AGC	AGC	—	—	—
VLx3	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CAG	GGT	GAT	CGT	GTG	ACC	ATT	AGC	AGC	—	—	—
VLx4	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CAG	GGT	GAT	CGT	GTG	ACC	ATT	AGC	AGC	—	—	—
VL11	GAT	ATC	GTG	CTG	ACC	CAG	CCG	CCT	—	TCA	GTG	AGT	GGC	GGA	CCA	GGT	—	—	—
VL12	GAT	ATC	GCA	CTG	ACC	CAG	CCA	GCT	—	TCA	GTG	AGC	GGC	TGA	CCA	GGT	—	—	—
VL13	GAT	ATC	GAA	CTG	ACC	CAG	CCG	CCT	—	TCA	GTG	AGC	GTT	GGA	CCA	GGT	—	—	—

VH

Framework 1																			
CDR 1																			
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
VH1A	CAG	GTG	CAA	TTG	GTT	CAG	TCT	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH1B	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH2	CAG	GTG	CAA	TTG	AAA	GAA	AGC	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH3	CAG	GTG	CAA	TTG	GTG	GAA	AGC	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH4	CAG	GTG	CAA	TTG	GTG	GAA	AGC	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH5	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GGC	GGC	GAA	GTG	AAA	AAA	AAA	CCG	GGC	AGC	AGC	GTG
VH6	CAG	GTG	CAA	TTG	CAA	CAG	TCT	GGT	GGT	CCG	GGC	CTG	GTG	AAA	CCG	GGC	AGC	AGC	GTG

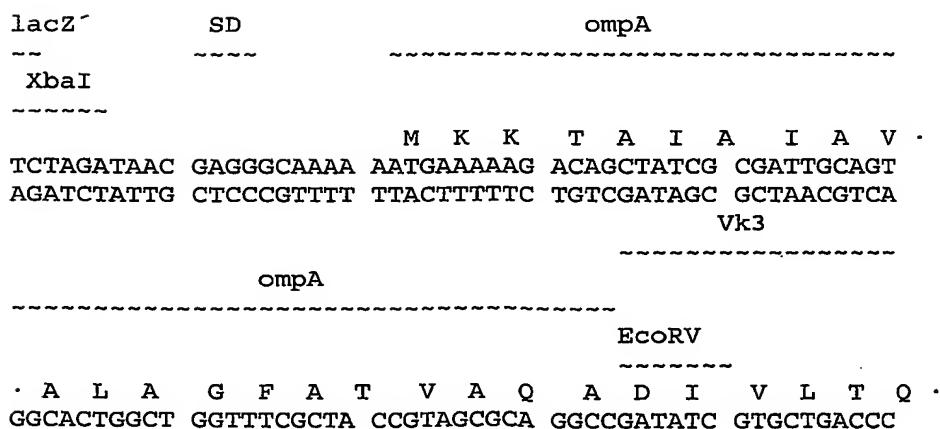
Framework 2

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Fig. 1b cont.

CDR 3										Framework 4									

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Fig. 2 cont.

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CCGTGACCGA CCAAAGCGAT GGCATCGCGT CCGGCTATAG CACGACTGGG
Vk3
-----
  S P A T L S L S P G E R A T L S
101 AGAGCCCGGC GACCCTGAGC CTGTCTCCGG GCGAACGTGC GACCCTGAGC
TCTCGGGCCG CTGGGACTCG GACAGAGGCC CGCTTGACAG CTGGGACTCG
Vk3
-----
  C R A S Q S V S S S Y L A W Y Q Q
151 TGCAGAGCGA GCCAGAGCGT GAGCAGCAGC TATCTGGCGT GGTACCAGCA
ACGTCTCGCT CGGTCTCGCA CTCGTCTGTCG ATAGACCGCA CCATGGTCGT
Vk3
-----
  K P G Q A P R L L I Y G A S S R A
201 GAAACCAGGT CAAGCACCGC GTCTATTAAT TTATGGCGCG AGCAGCCGTG
CTTTGGTCCA GTTCGTGGCG CAGATAATTA AATACCGCGC TCGTCGGCAC
Vk3
-----
  T G V P A R F S G S G S G T D F
251 CAACTGGGGT CCCGGCGCGT TTTAGCGGCT CTGGATCCGG CACGGATTTT
GTTGACCCCA GGGCCGCGCA AAATCGCCGA GACCTAGGCC GTGCCTAAAA
Vk3
-----
BbsI
-----
  T L T I S S L E P E D F A V Y Y C
301 ACCCTGACCA TTAGCAGCCT GGAACCTGAA GACTTTGCGG TGTATTATTG
TGGGACTGGT AATCGTCGGA CCTTGGACTT CTGAAACGCC ACATAATAAC
Vk3
-----
MscI
-----
  Q Q H Y T T P P T F G Q G T K V E
351 CCAGCAGCAT TATACCACCC CGCCGACCTT TGGCCAGGGT ACGAAAGTTG
GGTCGTCGTA ATATGGTGGG GCGGCTGGAA ACCGGTCCCA TGCTTTCAAC
CL kappa
-----
Vk3
-----
BsiWI
-----
  I K R T V A A P S V F I F P P S
401 AAATTAAACG TACGGTGGCT GCTCCGAGCG TGTTTATTTT TCCGCCGAGC
TTTAATTTGC ATGCCACCGA CGAGGCTCGC ACAAATAAAA AGGCGGCTCG
CL kappa
-----
  D E Q L K S G T A S V V C L L N N
451 GATGAACAAC TGAAAAGCGG CACGGCGAGC GTGGTGTGCC TGCTGAACAA
CTACTTGTTG ACTTTTCGCC GTGCCGCTCG CACCACACGG ACGACTTGTT
CL kappa
-----
  F Y P R E A K V Q W K V D N A L Q
501 CTTTATATCCG CGTGAAGCGA AAGTTCAGTG GAAAGTAGAC AACGCGCTGC
GAAAATAGGC GCACTTCGCT TTCAAGTCAC CTTTCATCTG TTGCGCGACG
CL kappa
-----
  S G N S Q E S V T E Q D S K D S
551 AAAGCGGCAA CAGCCAGGAA AGCGTGACCG AACAGGATAG CAAAGATAGC
TTTCGCCGTT GTCGGTCCTT TCGCACTGGC TTGTCCTATC GTTCTATCG
CL kappa
-----

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Fig. 2 cont.

```

      T Y S L S S T L T L S K A D Y E K .
601  ACCTATTCTC TGAGCAGCAC CCTGACCCTG AGCAAAGCGG ATTATGAAAA
      TGGATAAGAG ACTCGTCGTG GGA CTGGGAC TCGTTTCGCC TAATACTTTT
      CL kappa
      ~~~~~
      . H K V Y A C E V T H Q G L S S P V .
651  ACATAAAGTG TATGCGTGCG AAGTGACCCA TCAAGGTCTG AGCAGCCCCGG
      TGTATTTTAC ATACGCACGC TTCACTGGGT AGTTCCAGAC TCGTCGGGGCC
      CL kappa
      ~~~~~
      ~~~~~
      StuI          SphI
      ~~~~~
      . T K S F N R G E A
701  TGACTAAATC TTTTAATCGT GGCAGAGCCT GATAAGCATG CGTAGGAGAA
      ACTGATTTAG AAAATTAGCA CCGCTCCGGA CTATTCGTAC GCATCCTCTT
      phoA
      ~~~~~
      ~~~~~
      SapI
      ~~~~~
      M K Q S T I A L A L L P L L F .
751  AATAAAATGA AACAAAGCAC TATTGCACTG GCACTCTTAC CGTTGCTCTT
      TTATTTTACT TTGTTTCGTG ATAACGTGAC CGTGAGAATG GCAACGAGAA
      VH3
      ~~~~~
      phoA
      ~~~~~
      SapI          MfeI
      ~~~~~
      . T P V T K A Q V Q L V E S G G G L .
801  CACCCCTGTT ACCAAAGCCG AAGTGCAATT GGTGGAAAGC GGCGGCGGCC
      GTGGGGACAA TGGTTTCGGC TTCACGTAA CCACCTTTCG CCGCCGCCGG
      VH3
      ~~~~~
      . V Q P G G S L R L S C A A S G F
851  TGGTGCAACC GGGCGGCAGC CTGCGTCTGA GCTGCGCGGC CTCCGGATTT
      ACCACGTTGG CCCGCCGTCG GACGCAGACT CGACGCGCCG GAGGCCTAAA
      VH3
      ~~~~~
      T F S S Y A M S W V R Q A P G K G .
901  ACCTTTAGCA GCTATGCGAT GAGCTGGGTG CGCCAAGCCC CTGGGAAGGG
      TGGAAATCGT CGATACGCTA CTCGACCCAC GCGGTTTCGGG GACCCTTCCC
      VH3
      ~~~~~
      . L E W V S A I S G S G G S T Y Y A .
951  TCTCGAGTGG GTGAGCGCGA TTAGCGGTAG CGGCGGCAGC ACCTATTATG
      AGAGCTCACC CACTCGCGCT AATCGCCATC GCCGCCGTCG TGGATAATAC
      VH3
      ~~~~~
      ~~~~~
      PmlI
      ~~~~~
      . D S V K G R F T I S R D N S K N
1001 CGGATAGCGT GAAAGGCCGT TTTACCATT CACGTGATAA TTCGAAAAAC
      GCCTATCGCA CTTTCCGGCA AAATGGTAAA GTGCACTATT AAGCTTTTTT
      VH3
      ~~~~~
      T L Y L Q M N S L R A E D T A V Y .
1051 ACCCTGTATC TGCAATGAA CAGCCTGCGT GCGGAAGATA CGGCCGTGTA
      TGGGACATAG ACGTTTACTT GTCGGACGCA CGCCTTCTAT GCCGGCACAT
      VH3
      ~~~~~
      ~~~~~
      BssHII

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800S 2

9/43/94 Fig. 2 cont.

1101 . Y C A R W G G D G F Y A M D Y W G .
 TTATTGCGCG CGTTGGGGCG GCGATGGCTT TTATGCGATG GATTATTGGG
 AATAACGCGC GCAACCCCGC CGCTACCGAA AATACGCTAC CTAATAACCC
 CH1

VH3

SallI

StyI

BlnI

1151 . Q G T L V T V S S A S T K G P S
 GCCAAGGCAC CCTGGTGACG GTTAGCTCAG CGTCGACCAA AGGTCCAAGC
 CGGTTCCGTG GGACCACTGC CAATCGAGTC GCAGCTGGTT TCCAGGTTTC
 CH1

1201 V F P L A P S S K S T S G G T A A .
 GTGTTTCCGC TGGCTCCGAG CAGCAAAGC ACCAGCGGCG GCACGGCTGC
 CACAAAGGCG ACCGAGGCTC GTCGTTTTTCG TGGTCGCCGC CGTGCCGACG
 CH1

1251 . L G C L V K D Y F P E P V T V S W .
 CCTGGGCTGC CTGGTTAAAG ATTATTTCCC GGAACCAAGTC ACCGTGAGCT
 GGACCCGACG GACCAATTTT TAATAAAGG CTTGGTCAG TGGCACTCGA
 CH1

1301 . N S G A L T S G V H T F P A V L
 GGAACAGCGG GGCGCTGACC AGCGGCGTGC ATACCTTTCC GGCGGTGCTG
 CCTGTGCGCC CCGCGACTGG TCGCCGACG TATGGAAAGG CCGCCACGAC
 CH1

1351 Q S S G L Y S L S S V V T V P S S .
 CAAAGCAGCG GCCTGTATAG CCTGAGCAGC GTTGTGACCG TGCCGAGCAG
 GTTTCGTGCG CGGACATATC GGACTCGTCG CAACACTGGC ACGGCTCGTC
 CH1

1401 . S L G T Q T Y I C N V N H K P S N .
 CAGCTTAGGC ACTCAGACCT ATATTTGCAA CGTGAACCAT AAACCGAGCA
 GTCGAATCCG TGAGTCTGGA TATAAACGTT GCACTTGGTA TTTGGCTCGT
 CH1 CTgIII

EcoRI

1451 . T K V D K K V E P K S E F G G G
 ACACCAAAGT GGATAAAAAA GTGGAACCGA AAAGCGAATT CGGGGGAGGG
 TGTGGTTTCA CCTATTTTTT CACCTTGGCT TTTCGCTTAA GCCCCCTCCC
 CTgIII

1501 S G S G D F D Y E K M A N A N K G .
 AGCGGGAGCG GTGATTTTGA TTATGAAAAG ATGGCAAACG CTAATAAGGG
 TCGCCCTCGC CACTAAAACCT AATACTTTTC TACCGTTTGC GATTATTCCC
 CTgIII

1551 . A M T E N A D E N A L Q S D A K G .
 GGCTATGACC GAAAATGCCG ATGAAAACGC GCTACAGTCT GACGCTAAAG
 CCGATACTGG CTTTACGGC TACTTTTGCG CGATGTCAGA CTGCGATTTT
 CTgIII

1601 . K L D S V A T D Y G A A I D G F
 GCAAACCTTGA TTCTGTCGCT ACTGATTACG GTGCTGCTAT CGATGGTTTC

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Fig. 2 cont.

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CGTTTGAAGT AAGACAGCGA TGAATAATGC CACGACGATA GCTACCAAAG
CTgIII
-----
  I G D V S G L A N G N G A T G D F .
1651 ATTGGTGACG TTTCCGGCCT TGCTAATGGT AATGGTGCTA CTGGTGATTT
TAACCACTGC AAAGGCCGGA ACGATTACCA TTACCACGAT GACCACTAAA
CTgIII
-----
  A G S N S Q M A Q V G D G D N S P .
1701 TGCTGGCTCT AATTCCCAAA TGGCTCAAGT CGGTGACGGT GATAATTCAC
ACGACCGAGA TTAAGGGTTT ACCGAGTTCA GCCACTGCCA CTATTAAGTG
CTgIII
-----
  L M N N F R Q Y L P S L P Q S V
1751 CTTTAATGAA TAATTTCCTT CAATATTTAC CTTCCCTCCC TCAATCGGTT
GAAATTACTT ATTAAAGGCA GTTATAAATG GAAGGGAGGG AGTTAGCCAA
CTgIII
-----
  E C R P F V F G A G K P Y E F S I .
1801 GAATGTGCGC CTTTGTCTT TGGCGCTGGT AAACCATATG AATTTTCTAT
CTTACAGCGG GAAAACAGAA ACCGCGACCA TTTGGTATAC TTAAAAGATA
CTgIII
-----
  D C D K I N L F R G V F A F L L Y .
1851 TGATTGTGAC AAAATAAACT TATTCCTGGT TGTCTTTGCG TTTCTTTTAT
ACTAACACTG TTTTATTTGA ATAAGGCACC ACAGAAACGC AAAGAAAATA
CTgIII
-----
  V A T F M Y V F S T F A N I L R
1901 ATGTTGCCAC CTTTATGTAT GTATTTTCTA CGTTTGCTAA CATACTGCGT
TACAACGGTG GAAATACATA CATAAAAGAT GCAAACGATT GTATGACGCA
CTgIII
-----
                                Stop                lpp terminator
                                ---
                                HindIII
                                ~~~~~

  N K E S
1951 AATAAGGAGT CTTGATAAGC TTGACCTGTG AAGTGAAAAA TGGCGCAGAT
TTATTCCTCA GAACTATTCG AACTGGACAC TTCACTTTTT ACCGCGTCTA
lpp terminator
-----
2001 TGTGCGACAT TTTTFTTGTC TGCCGTTTAA TGAAATTGTA AACGTTAATA
ACACGCTGTA AAAAAACAG ACGGCAAATT ACTTTAACAT TTGCAATTAT
-----
                                f1 origin
2051 TTTTGTGTTAA ATTGCGGTTA AATTTTGTG AAATCAGCTC ATTTTAAAC
AAAACAATTT TAAGCGCAAT TTAAAAACAA TTTAGTCGAG TAAAAAATTG
-----
                                f1 origin
2101 CAATAGGCCG AAATCGGCAA AATCCCTTAT AAATCAAAAG AATAGACCGA
GTTATCCGGC TTTAGCCGTT TTAGGGAATA TTTAGTTTTT TTATCTGGCT
-----
                                f1 origin
2151 GATAGGGTTG AGTGTGTGTC CAGTTTGGAA CAAGAGTCCA CTATTAAAGA
CTATCCCAAC TCACAACAAG GTCAAACCTT GTTCTCAGGT GATAATTTCT
-----
                                f1 origin
2201 ACGTGGACTC CAACGTCAAA GGGCGAAAAA CCGTCTATCA GGGCGATGGC
TGCACCTGAG GTTGCAGTTT CCCGCTTTTT GGCAGATAGT CCCGCTACCG
-----

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f1 origin

T->A

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f1 origin
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f1 origin
```

f1 origin

f1 origin

f1 origin

COLEI

COLEI

ORI

COLEI

COLET

COLEI

mutation

COLEI

mutation

COLEI

mutation

COLEI

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Fig. 2 cont.

```

2851  GTAACATATCG TCTTGAGTCC AACCCGGTAA GACACGACTT ATCGCCACTG
      CATTGATAGC AGAACTCAGG TTGGGCCATT CTGTGCTGAA TAGCGGTGAC
      ~~~~~
                        ColEI
2901  GCAGCAGCCA CTGGTAACAG GATTAGCAGA GCGAGGTATG TAGGCGGTGC
      CGTCGTCGGT GACCATTGTC CTAATCGTCT CGCTCCATAC ATCCGCCACG
      ~~~~~
                        ColEI
                                          mutation
2951  TACAGAGTTC TTGAAGTGGT GGCCTAACTA CGGCTACACT AGAAGAACAG
      ATGTCTCAAG AACTTCACCA CCGGATTGAT GCCGATGTGA TCTTCTTGTC
      ~~~~~
                        ColEI
                        mutation
3001  TATTTGGTAT CTGCGCTCTG CTGTAGCCAG TTACCTTCGG AAAAAGAGTT
      ATAAACCATA GACGCGAGAC GACATCGGTC AATGGAAGCC TTTTCTCA
      ~~~~~
                        ColEI
3051  GGTAGCTCTT GATCCGGCAA ACAAAACCACC GCTGGTAGCG GTGGTTTTTT
      CCATCGAGAA CTAGGCCGTT TGTTTGGTGG CGACCATCGC CACCAAAAAA
      ~~~~~
                        ColEI
3101  TGTTTGCAAG CAGCAGATTA CGCGCAGAAA AAAAGGATCT CAAGAAGATC
      ACAACGTTT GTCGTCTAAT GCGCGTCTTT TTTTCCTAGA GTTCTTCTAG
      ~~~~~
                        ColEI
3151  CTTTGATCTT TTCTACGGGG TCTGACGCTC AGTGGAACGA AACTCACGT
      GAAACTAGAA AAGATGCCCC AGACTGCGAG TCACCTTGCT TTTGAGTGCA
      ~~~~~
                        ColEI
                                          cat terminator
                        ~~~~~
                        BglII
                        ~~~~~
3201  TAAGGGATTT TGGTCAGATC TAGCACCAGG CGTTTAAGGG CACCAATAAC
      ATTCCCTAAA ACCAGTCTAG ATCGTGGTCC GCAAATTCCC GTGGTTATTG
      ~~~~~
                        ColEI
                        cat terminator
                        ~~~~~
3251  TGCCTTAAAA AAATTACGCC CCGCCCTGCC ACTCATCGCA GTACTGTTGT
      ACGGAATTTT TTAATGCGG GCGGGGACGG TGAGTAGCGT CATGACAACA
      ~~~~~
                        CM (R)
3301  AATTCATTAA GCATTCTGCC GACATGGAAG CCATCACAAA CGGCATGATG
      TTAAGTAATT CGTAAGACGG CTGTACCTTC GGTAGTGTTT GCCGTACTAC
      ~~~~~
                        CM (R)
3351  AACCTGAATC GCCAGCGGCA TCAGCACCTT GTCGCCTTGC GTATAATATT
      TTGGACTTAG CGGTCGCCGT AGTCGTGGAA CAGCGGAACG CATATTATAA
      ~~~~~
                        CM (R)
3401  TGCCCATAGT GAAAACGGGG GCGAAGAAGT TGTCCATATT GGCTACGTTT
      ACGGGTATCA CTTTTGCCCC CGCTTCTTCA ACAGGTATAA CCGATGCAAA
      ~~~~~
                        CM (R)
3451  AAATCAAAAC TGGTGAAACT CACCCAGGGA TTGGCTGAGA CGAAAAACAT
      TTTAGTTTTG ACCACTTTGA GTGGGTCCCT AACCGACTCT GCTTTTTTGA
      ~~~~~

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Fig. 2 cont.

```

CM (R)
3501  ATTCTCAATA AACCCCTTTAG GGAAATAGGC CAGGTTTTTCA CCGTAACACG
      TAAGAGTTAT TTGGGAAATC CCTTTATCCG GTCCAAAAGT GGCATTGTGC
      ~~~~~
CM (R)
3551  CCACATCTTG CGAATATATG TGTAAGAACT GCCGGAAAATC GTCGTGGTAT
      GGTGTAGAAC GCTTATATAC ACATCTTTGA CGGCCTTTAG CAGCACCATA
      ~~~~~
CM (R)
3601  TCACTCCAGA GCGATGAAAA CGTTTCAGTT TGCTCATGGA AAACGGTGTA
      AGTGAGGTCT CGCTACTTTT GCAAAGTCAA ACGAGTACCT TTTGCCACAT
      ~~~~~
CM (R)
3651  ACAAGGGTGA ACACTATCCC ATATCACCAG CTCACCGTCT TTCATTGCCA
      TGTTCCTCACT TGTGATAGGG TATAGTGGTC GAGTGGCAGA AAGTAACGGT
      ~~~~~
CM (R)
3701  TACGGAACTC CGGGTGAGCA TTCATCAGGC GGGCAAGAAT GTGAATAAAG
      ATGCCTTGAG GCCCACTCGT AAGTAGTCCG CCCGTTCTTA CACTTATTTT
      ~~~~~
CM (R)
3751  GCCGGATAAA ACTTGTGCTT ATTTTCTTTT ACGGTCTTTA AAAAGGCCGT
      CGGCCTATTT TGAACACGAA TAAAAAGAAA TGCCAGAAAT TTTTCCGGCA
      ~~~~~
CM (R)
3801  AATATCCAGC TGAACGGTCT GGTATAGGT ACATTGAGCA ACTGACTGAA
      TTATAGGTCG ACTTGCCAGA CCAATATCCA TGTAACCTCGT TGAAGTACTT
      ~~~~~
CM (R)
3851  ATGCCTCAAA ATGTTCTTTA CGATGCCATT GGGATATATC AACGGTGGTA
      TACGGAGTTT TACAAGAAAT GCTACGGTAA CCCTATATAG TTGCCACCAT
      ~~~~~
CM (R)
3901  TATCCAGTGA TTTTTTCTC CATTTTAGCT TCCTTAGCTC CTGAAAATCT
      ATAGGTCACT AAAAAAGAG GTAAAATCGA AGGAATCGAG GACTTTTAGA
      ~~~~~
      CM (R)                                SD
      ~~~~~
                                cat promoter
3951  CGATAACTCA AAAAATACGC CCGGTAGTGA TCTTATTTCA TTATGGTGAA
      GCTATTGAGT TTTTATGCG GGCCATCACT AGAATAAAGT AATACCACTT
      ~~~~~
                                cat promoter
                                CRP site
                                ~~~~~
4001  AGTTGGAACC TCACCCGACG TCTAATGTGA GTTAGCTCAC TCATTAGGCA
      TCAACCTTGG AGTGGGCTGC AGATTACACT CAATCGAGTG AGTAATCCGT
      ~~~~~
      cat promoter                                lac mRNA
      start
                                                    ~
                                                    lac operator
                                                    ~~~~~
      -35 region                                -10 region
      ~~~~~                                ~~~~~
4051  CCCCAGGCTT TACTTTTAT GCTTCCGGCT CGTATGTTGT GTGGAATTGT
      GGGGTCCGAA ATGTGAAATA CGAAGGCCGA GCATACAACA CACCTTAACA
      lac operator                                SD                                lacZ'
      ~~~~~                                ~~~~~
4101  GAGCGGATAA CAATTTTACA CAGGAAACAG CTATGACCAT GATTACGAAT

```

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Fig. 2 cont.

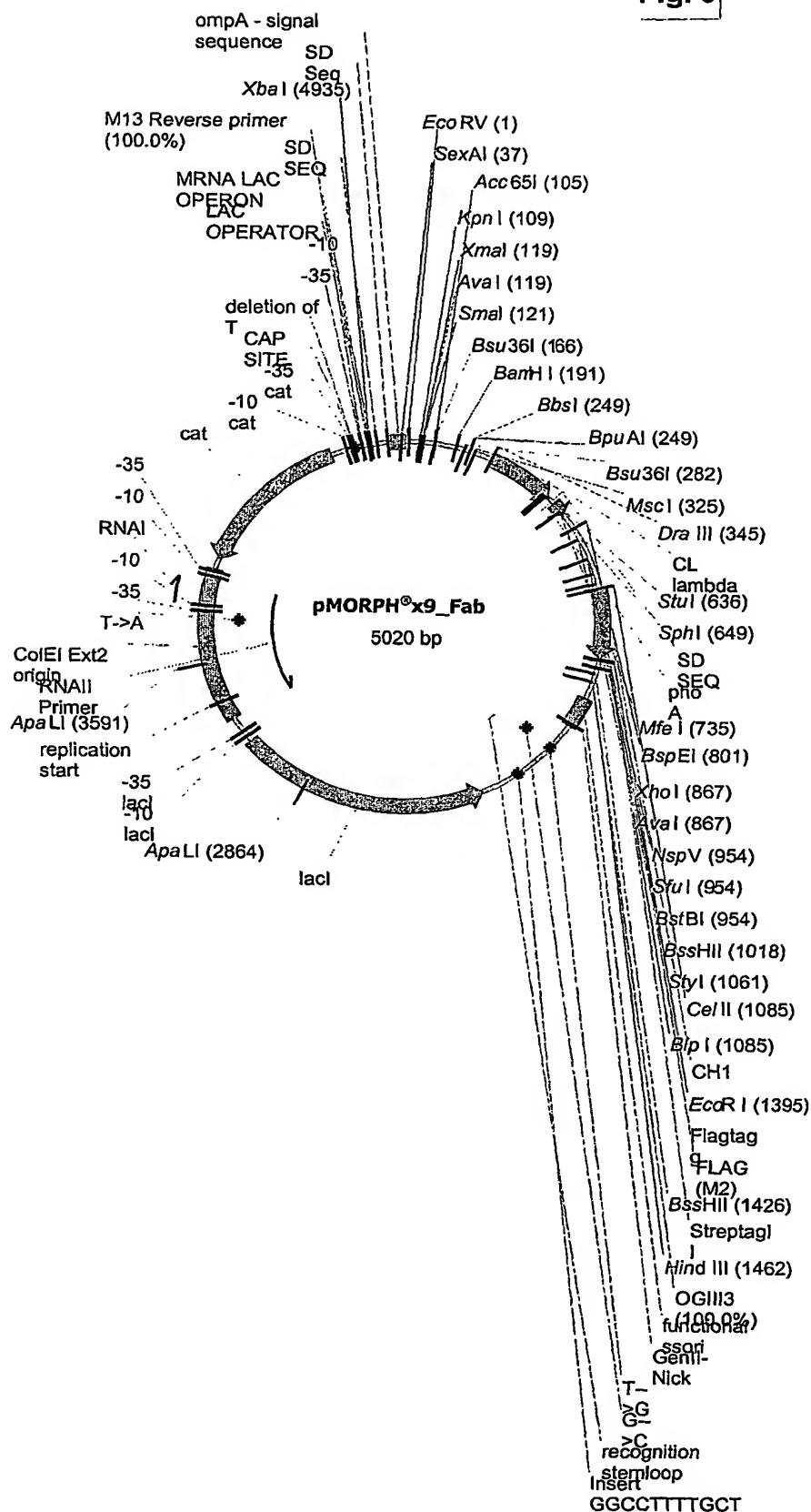
CTCGCCTATT GTTAAAGTGT GTCCTTTGTC GATACTGGTA CTAATGCTTA
lacZ⁻

4151

-
T
A

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Fig. 3



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Fig. 3 cont.

EcoRV

SexAI

```

1  ATCGTGCTGA CCCAGCCGCC TTCAGTGAGT GGCGCACCAG GTCAGCGTGT
   TAGCACGACT GGGTCGGCGG AAGTCACTCA CCGCGTGGTC CAGTCGCACA

51  GACCATCTCG TGTAGCGGCA GCAGCAGCAA CATTGGCAGC AACTATGTGA
    CTGGTAGAGC ACATCGCCGT CGTCGTCTGT GTAACCGTCG TTGATACACT

```

XmaI

KpnI

SmaI

Acc65I

AvaI

```

101 GCTGGTACCA GCAGTTGCCC GGGACGGCGC CGAAACTGCT GATTTATGAT
    CGACCATGGT CGTCAACGGG CCCTGCCGCG GCTTTGACGA CTAAATACTA

```

Bsu36I

BamHI

```

151 AACAAACCAGC GTCCCTCAGG CGTGCCGGAT CGTTTTAGCG GATCCAAAAG
    TTGTTGGTCG CAGGGAGTCC GCACGGCCTA GCAAATCGC CTAGGTTTTC

```

BpuAI

BbsI

```

201 CGGCACCAGC GCGAGCCTTG CGATTACGGG CCTGCAAAGC GAAGACGAAG
    GCCGTGGTCG CGCTCGGAAC GCTAATGCCG GGACGTTTCG CTTCTGCTTC

```

Bsu36I

```

251 CGGATTATTA TTGCCAGAGC TATGACATGC CTCAGGCTGT GTTTGGCGGC
    GCCTAATAAT AACGGTCTCG ATACTGTACG GAGTCCGACA CAAACCGCCG

```

MscI

DraIII

```

301 GGCACGAAGT TTAACCGTTC TTGGCCAGCC GAAAGCCGCA CCGAGTGTGA
    CCGTGCTTCA AATTGGCAAG AACCGGTCGG CTTTCGGCGT GGCTCACACT

351 CGCTGTTTCC GCCGAGCAGC GAAGAATTGC AGGCGAACAA AGCGACCCTG
    GCGACAAAGG CGGCTCGTCG CTTCTTAACG TCCGCTTGTT TCGCTGGGAC

401 GTGTGCCTGA TTAGCGACTT TTATCCGGGA GCCGTGACAG TGGCCTGGAA
    CACACGGACT AATCGCTGAA AATAGGCCCT CGGCACTGTC ACCGGACCTT

451 GGCAGATAGC AGCCCCGTCA AGGCGGGAGT GGAGACCACC ACACCCTCCA
    CCGTCTATCG TCGGGGCAGT TCCGCCCTCA CCTCTGGTGG TGTGGGAGGT

501 AACAAAGCAA CAACAAGTAC GCGGCCAGCA GCTATCTGAG CCTGACGCCT
    TTGTTTCGTT GTTGTTTCATG CGCCGGTCGT CGATAGACTC GGACTGCGGA

551 GAGCAGTGGA AGTCCCACAG AAGCTACAGC TGCCAGGTCA CGCATGAGGG
    CTCGTCACCT TCAGGGTGTC TTCGATGTCT ACGGTCCAGT GCGTACTCCC

```


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Fig. 3 cont.

StuI

SphI

~~~~~

~~~~~

601 GAGCACCGTG GAAAAAACCG TTGCGCCGAC TGAGGCCTGA TAAGCATGCG
CTCGTGGCAC CTTTTTTGGC AACGCGGCTG ACTCCGGACT ATTCGTACGC

651 TAGGAGAAAA TAAAATGAAA CAAAGCACTA TTGCACTGGC ACTCTTACCG
ATCCTCTTTT ATTTTACTTT GTTTCGTGAT AACGTGACCG TGAGAATGGC

MfeI

~~~~~

701 TTGCTCTTCA CCCCTGTTAC CAAAGCCCAG GTGCAATTGA AAGAAAGCGG  
AACGAGAAGT GGGGACAATG GTTTCGGGTC CACGTAACT TTCTTTCGCC

BspEI

~

751 CCCGGCCCTG GTGAAACCGA CCCAAACCCT GACCCTGACC TGTACCTTTT  
GGGCCGGGAC CACTTTGGCT GGGTTTGGGA CTGGGACTGG ACATGGAAAA

BspEI

~~~~~

801 CCGGATTTAG CCTGTCCACG TCTGGCGTTG GCGTGGGCTG GATTCGCCAG
GGCCTAAATC GGACAGGTGC AGACCGCAAC CGCACCCGAC CTAAGCGGTC

XhoI

~~~~~

AvaI

~~~~~

851 CCGCCTGGGA AAGCCCTCGA GTGGCTGGCT CTGATTGATT GGGATGATGA
GGCGGACCCT TTCGGGAGCT CACCGACCGA GACTAACTAA CCCTACTACT

901 TAAGTATTAT AGCACCAGCC TGAAAACGCG TCTGACCATT AGCAAAGATA
ATTCATAATA TCGTGGTCGG ACTTTTGCGC AGACTGGTAA TCGTTTCTAT

BstBI

~~~~~

SfuI

~~~~~

NspV

~~~~~

951 CTTCGAAAAA TCAGGTGGTG CTGACTATGA CCAACATGGA CCCGGTGGAT  
GAAGCTTTTT AGTCCACCAC GACTGATACT GGTGTACCT GGGCCACCTA

BssHII

~~~~~

1001 ACGGCCACCT ATTATTGCGC GCGTTCTCCT CGTTATCGTG GTGCTTTTGA
TGCCGGTGGA TAATAACGCG CGCAAGAGGA GCAATAGCAC CACGAAAACCT

BlpI

~~~~~

StyI

~~~~~

CelII

~~~~~

1051 TTATTGGGGC CAAGGCACCC TGGTGACGGT TAGCTCAGCG TCGACCAAAG  
AATAACCCCG GTTCCGTGGG ACCACTGCCA ATCGAGTCGC AGCTGGTTTC

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Fig. 3 cont.

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1101  GTCCAAGCGT  GTTTCCGCTG  GCTCCGAGCA  GCAAAAGCAC  CAGCGGCGGC
      CAGGTTTCGCA  CAAAGGCGAC  CGAGGCTCGT  CGTTTTTCGTG  GTCGCCGCCG

1151  ACGGCTGCCC  TGGGCTGCCT  GGTAAAGAT  TATTTCCCGG  AACCAGTCAC
      TGCCGACGGG  ACCCGACGGA  CCAATTTCTA  ATAAAGGGCC  TTGGTCAGTG

1201  CGTGAGCTGG  AACAGCGGGG  CGCTGACCAG  CGGCGTGCAT  ACCTTTCCGG
      GCACTCGACC  TTGTCGCCCC  GCGACTGGTC  GCCGCACGTA  TGGAAAGGCC

1251  CGGTGCTGCA  AAGCAGCGGC  CTGTATAGCC  TGAGCAGCGT  TGTGACCGTG
      GCCACGACGT  TTCGTCGCCG  GACATATCGG  ACTCGTCGCA  AACTGGCAC

1301  CCGAGCAGCA  GCTTAGGCAC  TCAGACCTAT  ATTTGCAACG  TGAACCATAA
      GGCTCGTCGT  CGAATCCGTG  AGTCTGGATA  TAAACGTTGC  ACTTGGTATT

                                     EcoRI
                                     ~~~~~~
1351 ACCGAGCAAC ACCAAAGTGG ATAAAAAAGT GGAACCGAAA AGCGAATTCG
 TGGCTCGTTG TGGTTTCACC TATTTTTTCA CCTTGGCTTT TCGCTTAAGC

 BssHII
                                     ~~~~~~
1401  ACTATAAAGA  TGACGATGAC  AAAGGCGCGC  CGTGGAGCCA  CCCGCAGTTT
      TGATATTTCT  ACTGCTACTG  TTTCCGCGCG  GCACCTCGGT  GGGCGTCAAA

                                     HindIII
                                     ~~~~~~
1451 GAAAAATGAT AAGCTTGACC TGTGAAGTGA AAAATGGCGC AGATTGTGCG
 CTTTTTACTA TTCGAACTGG AACTTCACT TTTTACCGCG TCTAACACGC

 OGIII3 100.0%
 =====

1501 ACATTTTTTT TGTCTGCCGT TTAATTAAAG GGGGGGGGGG GCCGGCCTGG
 TGTAAAAAAA ACAGACGGCA AATTAATTTT CCCCCCCCCC CGGCCGGACC

1551 GGGGGGGTGT ACATGAAATT GTAAACGTTA ATATTTTGT AAAATTCGCG
 CCCCCCACCA TGTACTTTAA CATTTGCAAT TATAAAACAA TTTTAAGCGC

1601 TTAAATTTTT GTTAAATCAG CTCATTTTTT AACCAATAGG CCGAAATCGG
 AATTTAAAAA CAATTTAGTC GAGTAAAAAA TTGGTTATCC GGCTTTAGCC

1651 CAAAATCCCT TATAAATCAA AAGAATAGAC CGAGATAGGG TTGAGTGTTG
 GTTTTAGGGA ATATTTAGTT TTCTTATCTG GCTCTATCCC AACTCACAAC

1701 TTCCAGTTTG GAACAAGAGT CCACTATTAA AGAACGTGGA CTCCAACGTC
 AAGGTCAAAC CTTGTTCTCA GGTGATAATT TCTTGACCT GAGGTTGCAG

1751 AAAGGGCGAA AAACCGTCTA TCAGGGCGAT GGCCCACTAC GAGAACCATC
 TTTCCCGCTT TTTGGCAGAT AGTCCCGCTA CCGGGTGATG CTCTTGGTAG

1801 ACCCTAATCA AGTTTTTTTG GGTCGAGGTG CCGTAAAGCA CTAAATCGGA
 TGGGATTAGT TCAAAAAACC CCAGCTCCAC GGCATTTCTG GATTTAGCCT

```

## 19/43 Fig. 3 cont.

1851 ACCCTAAAGG GAGCCCCCGA TTTAGAGCTT GACGGGGAAA GCCGGCGAAC  
TGGGATTTCC CTCGGGGGCT AAATCTCGAA CTGCCCCCTT CGGCCGCTTG

1901 GTGGCGAGAA AGGAAGGGAA GAAAGCGAAA GGAGCGGGCG CTAGGGCGCT  
CACCGCTCTT TCCTTCCCTT CTTTCGCTTT CCTCGCCCGC GATCCCGCGA

1951 GGCAAGTGTA GCGGTCACGC TCGCGGTAAC CACCACACCC GCCGCGCTTA  
CCGTTACAT CGCCAGTGCG ACGCGCATTG GTGGTGTGGG CGGCGCGAAT

2001 ATGCGCCGCT ACAGGGCGCG TGCTAGACTA GTGTTTAAAC CGGACCGGGG  
TACGCGGCGA TGTCCCGCGC ACGATCTGAT CACAAATTTG GCCTGGCCCC

2051 GGGGGCTTAA GTGGGCTGCA AAACAAAACG GCCTCCTGTC AGGAAGCCGC  
CCCCGAATT CACCCGACGT TTTGTTTTGC CGGAGGACAG TCCTTCGGCG

2101 TTTTATCGGG TAGCCTCACT GCCCGCTTTC CAGTCGGGAA ACCTGTCGTG  
AAAATAGCCC ATCGGAGTGA CGGGCGAAAG GTCAGCCCTT TGGACAGCAC

2151 CCAGCTGCAT CAGTGAATCG GCCAACGCGC GGGGAGAGGC GGTTTGCGTA  
GGTCGACGTA GTCACCTAGC CGGTTGCGCG CCCCTCTCCG CCAAACGCAT

2201 TTGGGAGCCA GGGTGGTTTT TCTTTTCACC AGTGAGACGG GCAACAGCTG  
AACCCTCGGT CCCACCAAAA AGAAAAGTGG TCACTCTGCC CGTTGTCGAC

2251 ATTGCCCTTC ACCGCCTGGC CCTGAGAGAG TTGCAGCAAG CGGTCCACGC  
TAACGGGAAG TGGCGGACCG GGACTCTCTC AACGTCGTTT GCCAGGTGCG

2301 TGGTTTGCCC CAGCAGGCGA AAATCCTGTT TGATGGTGGT CAGCGGCGGG  
ACCAAACGGG GTCGTCCGCT TTTAGGACAA ACTACCACCA GTCGCCGCCC

2351 ATATAACATG AGCTGTCCTC GGTATCGTCG TATCCCACTA CCGAGATGTC  
TATATTGTAC TCGACAGGAG CCATAGCAGC ATAGGGTGAT GGCTCTACAG

2401 CGCACCAACG CGCAGCCCGG ACTCGGTAAT GGCACGCATT GCGCCCAGCG  
GCGTGGTTGC GCGTCGGGCC TGAGCCATTA CCGTGCGTAA CGCGGGTCGC

2451 CCATCTGATC GTTGGCAACC AGCATCGCAG TGGGAACGAT GCCCTCATTC  
GGTAGACTAG CAACCGTTGG TCGTAGCGTC ACCCTTGCTA CGGGAGTAAG

2501 AGCATTTGCA TGGTTTGTG AAAACCGGAC ATGGCACTCC AGTCGCCTTC  
TCGTAAACGT ACCAAACAAC TTTTGGCCTG TACCGTGAGG TCAGCGGAAG

2551 CCGTTCCGCT ATCGGCTGAA TTTGATTGCG AGTGAGATAT TTATGCCAGC  
GGCAAGGCGA TAGCCGACTT AAAC TAACGC TCACTCTATA AATACGGTCG

2601 CAGCCAGACG CAGACGCGCC GAGACAGAAC TTAATGGGCC AGCTAACAGC  
GTCGGTCTGC GTCTGCGCGG CTCTGTCTTG AATTACCCGG TCGATTGTGCG

2651 GCGATTTGCT GGTGGCCCAA TCGGACCAGA TGCTCCACGC CCAGTCGCGT  
CGCTAAACGA CCACCGGGTT ACGCTGGTCT ACGAGGTGCG GGTCAGCGCA

2701 ACCGTCCTCA TGGGAGAAAA TAATACTGTT GATGGGTGTC TGGTCAGAGA  
TGGCAGGAGT ACCCTCTTTT ATTATGACAA CTACCCACAG ACCAGTCTCT

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Fig. 3 cont.

|      |                |            |            |             |             |
|------|----------------|------------|------------|-------------|-------------|
| 2751 | CATCAAGAAA     | TAACGCCGGA | ACATTAGTGC | AGGCAGCTTC  | CACAGCAATA  |
|      | GTAGTTCTTT     | ATTGCGGCCT | TGTAATCACG | TCCGTCTGAAG | GTGTCTGTTAT |
| 2801 | GCATCCTGGT     | CATCCAGCGG | ATAGTTAATA | ATCAGCCCCAC | TGACACGTTG  |
|      | GTAGGACCA      | GTAGGTCGCC | TATCAATTAT | TAGTCGGGTG  | ACTGTGCAAC  |
|      | ApaLI<br>~~~~~ |            |            |             |             |
| 2851 | CGCGAGAAGA     | TTGTGCACCG | CCGCTTTACA | GGCTTCGACG  | CCGCTTCGTT  |
|      | GCGCTCTTCT     | AACACGTGGC | GGCGAAATGT | CCGAAGCTGC  | GGCGAAGCAA  |
| 2901 | CTACCATCGA     | CACGACCACG | CTGGCACCCA | GTTGATCGGC  | GCGAGATTTA  |
|      | GATGGTAGCT     | GTGCTGGTGC | GACCGTGGGT | CAACTAGCCG  | CGCTCTAAAT  |
| 2951 | ATCGCCGCGA     | CAATTTGCGA | CGGCGCGTGC | AGGGCCAGAC  | TGGAGGTGGC  |
|      | TAGCGGCGCT     | GTTAAACGCT | GCCGCGCACG | TCCCGGTCTG  | ACCTCCACCG  |
| 3001 | AACGCCAATC     | AGCAACGACT | GTTTGCCCGC | CAGTTGTTGT  | GCCACGCGGT  |
|      | TTGCGGTTAG     | TCGTTGCTGA | CAAACGGGCG | GTCAACAACA  | CGGTGCGCCA  |
| 3051 | TAGGAATGTA     | ATTCAGCTCC | GCCATCGCCG | CTTCCACTTT  | TTCCCGCGTT  |
|      | ATCCTTACAT     | TAAGTCGAGG | CGGTAGCGGC | GAAGGTGAAA  | AAGGGCGCAA  |
| 3101 | TTCGCAGAAA     | CGTGGCTGGC | CTGGTTCACC | ACGCGGGAAA  | CGGTCTGATA  |
|      | AAGCGTCTTT     | GCACCGACCG | GACCAAGTGG | TGCGCCCTTT  | GCCAGACTAT  |
| 3151 | AGAGACACCG     | GCATACTCTG | CGACATCGTA | TAACGTTACT  | GGTTTCACAT  |
|      | TCTCTGTGGC     | CGTATGAGAC | GCTGTAGCAT | ATTGCAATGA  | CCAAAGTGTA  |
| 3201 | TCACCACCCT     | GAATTGACTC | TCTTCCGGGC | GCTATCATGC  | CATACCGCGA  |
|      | AGTGGTGGGA     | CTTAAGTGGG | AGAAGGCCCG | CGATAGTACG  | GTATGGCGCT  |
| 3251 | AAGGTTTTGC     | GCCATTCGAT | GCTAGCCATG | TGAGCAAAAAG | GCCAGCAAAA  |
|      | TTCCAAAACG     | CGGTAAGCTA | CGATCGGTAC | ACTCGTTTTT  | CGGTCTGTTT  |
| 3301 | GGCCAGGAAC     | CGTAAAAAGG | CCGCGTTGCT | GGCGTTTTTC  | CATAGGCTCC  |
|      | CCGGTCCTTG     | GCATTTTTTC | GGCGCAACGA | CCGCAAAAAG  | GTATCCGAGG  |
| 3351 | GCCCCCTGA      | CGAGCATCAC | AAAAATCGAC | GCTCAAGTCA  | GAGGTGGCGA  |
|      | CGGGGGGACT     | GCTCGTAGTG | TTTTTAGCTG | CGAGTTCAGT  | CTCCACCGCT  |
| 3401 | AACCCGACAG     | GACTATAAAG | ATACCAGGCG | TTTCCCCCTG  | GAAGCTCCCT  |
|      | TTGGGCTGTC     | CTGATATTTT | TATGGTCCGC | AAAGGGGGAC  | CTTCGAGGGA  |
| 3451 | CGTGCGCTCT     | CCTGTTCCGA | CCCTGCCGCT | TACCGGATAC  | CTGTCCGCCT  |
|      | GCACGCGAGA     | GGACAAGGCT | GGGACGGCGA | ATGGCCTATG  | GACAGGCGGA  |
| 3501 | TTCTCCCTTC     | GGGAAGCGTG | GCGCTTTCTC | ATAGCTCACG  | CTGTAGGTAT  |
|      | AAGAGGGAAG     | CCCTTCGCAC | CGCGAAAGAG | TATCGAGTGC  | GACATCCATA  |
|      | ApaLI<br>~~~~~ |            |            |             |             |
| 3551 | CTCAGTTCGG     | TGTAGGTCGT | TCGCTCCAAG | CTGGGCTGTG  | TGCACGAACC  |
|      | GAGTCAAGCC     | ACATCCAGCA | AGCGAGGTTC | GACCCGACAC  | ACGTGCTTGG  |

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Fig. 3 cont.

|      |             |            |             |             |             |
|------|-------------|------------|-------------|-------------|-------------|
| 3601 | CCCCGTTTCAG | CCCGACCGCT | GCGCCTTATC  | CGGTAACATAT | CGTCTTGAGT  |
|      | GGGGCAAGTC  | GGGCTGGCGA | CGCGGAATAG  | GCCATTGATA  | GCAGAACTCA  |
| 3651 | CCAACCCGGT  | AAGACACGAC | TTATCGCCAC  | TGGCAGCAGC  | CACTGGTAAC  |
|      | GGTTGGGCCA  | TTCTGTGCTG | AATAGCGGTG  | ACCGTCGTGC  | GTGACCATTG  |
| 3701 | AGGATTAGCA  | GAGCGAGGTA | TGTAGGCGGT  | GCTACAGAGT  | TCTTGAAGTG  |
|      | TCCTAATCGT  | CTCGCTCCAT | ACATCCGCCA  | CGATGTCTCA  | AGAACTTCAC  |
| 3751 | GTGGCCTAAC  | TACGGCTACA | CTAGAAGAAC  | AGTATTTGGT  | ATCTGCGCTC  |
|      | CACCGGATTG  | ATGCCGATGT | GATCTTCTTG  | TCATAAACCA  | TAGACGCGAG  |
| 3801 | TGCTGTAGCC  | AGTTACCTTC | GGAAAAAGAG  | TTGGTAGCTC  | TTGATCCGGC  |
|      | ACGACATCGG  | TCAATGGAAG | CCTTTTTTCTC | AACCATCGAG  | AACTAGGCCG  |
| 3851 | AAACAAACCA  | CCGCTGGTAG | CGGTGGTTTT  | TTTGTTTGCA  | AGCAGCAGAT  |
|      | TTTGTTTGGT  | GGCGACCATC | GCCACCAAAA  | AAACAAACGT  | TCGTCTGCTA  |
| 3901 | TACGCGCAGA  | AAAAAAGGAT | CTCAAGAAGA  | TCCTTTGATC  | TTTTCTACGG  |
|      | ATGCGCGTCT  | TTTTTTCCTA | GAGTTCTTCT  | AGGAAACTAG  | AAAAGATGCC  |
| 3951 | GGTCTGACGC  | TCAGTGGAAC | GAAAACTCAC  | GTTAAGGGAT  | TTTGGTCAGA  |
|      | CCAGACTGCG  | AGTCACCTTG | CTTTTGAGTG  | CAATTCCTTA  | AAACCAGTCT  |
| 4001 | TCTAGCACCA  | GGCGTTTAAG | GGCACCAATA  | ACTGCCTTAA  | AAAAATTACG  |
|      | AGATCGTGGT  | CCGCAAATTC | CCGTGGTTAT  | TGACGGAATT  | TTTTTAATGC  |
| 4051 | CCCCGCCCTG  | CCACTCATCG | CAGTACTGTT  | GTAATTCATT  | AAGCATTTCTG |
|      | GGGGCGGGAC  | GGTGAGTAGC | GTCATGACAA  | CATTAAGTAA  | TTCGTAAGAC  |
| 4101 | CCGACATGGA  | AGCCATCACA | AACGGCATGA  | TGAACCTGAA  | TCGCCAGCGG  |
|      | GGCTGTACCT  | TCGGTAGTGT | TTGCCGTACT  | ACTTGGACTT  | AGCGGTCGCC  |
| 4151 | CATCAGCACC  | TTGTGCGCTT | GCGTATAATA  | TTTGCCCATA  | GTGAAAACGG  |
|      | GTAGTCGTGG  | AACAGCGGAA | CGCATATTAT  | AAACGGGTAT  | CACTTTTGCC  |
| 4201 | GGGCGAAGAA  | GTTGTCCATA | TTGGCTACGT  | TTAAATCAAA  | ACTGGTGAAA  |
|      | CCCGCTTCTT  | CAACAGGTAT | AACCGATGCA  | AATTTAGTTT  | TGACCACTTT  |
| 4251 | CTCACCCAGG  | GATTGGCTGA | GACGAAAAAC  | ATATTCTCAA  | TAAACCCTTT  |
|      | GAGTGGGTCC  | CTAACCGACT | CTGCTTTTTG  | TATAAGAGTT  | ATTTGGGAAA  |
| 4301 | AGGGAAATAG  | GCCAGGTTTT | CACCGTAACA  | CGCCACATCT  | TGCGAATATA  |
|      | TCCCTTTATC  | CGGTCCAAAA | GTGGCATTGT  | GCGGTGTAGA  | ACGCTTATAT  |
| 4351 | TGTGTAGAAA  | CTGCCGGAAG | TCGTCTGGGT  | ATTCACCTCA  | GAGCGATGAA  |
|      | ACACATCTTT  | GACGGCCTTT | AGCAGCACCA  | TAAGTGAGGT  | CTCGCTACTT  |
| 4401 | AACGTTTCAG  | TTTGCTCATG | GAAAACGGTG  | TAACAAGGGT  | GAACACTATC  |
|      | TTGCAAAGTC  | AAACGAGTAC | CTTTTGCCAC  | ATTGTTCCCA  | CTTGTGATAG  |
| 4451 | CCATATCACC  | AGCTCACCGT | CTTTCATTGC  | CATACGGAAC  | TCCGGGTGAG  |
|      | GGTATAGTGG  | TCGAGTGGCA | GAAAGTAACG  | GTATGCCTTG  | AGGCCCACTC  |

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Fig. 3 cont.

4501 CATTTCATCAG GCGGGCAAGA ATGTGAATAA AGGCCGGATA AACTTTGTGC  
GTAAGTAGTC CGCCCGTTCT TACTTATT TCCGGCCTAT TTTGAACACG

4551 TTATTTTTTCT TTACGGTCTT TAAAAAGGCC GTAATATCCA GCTGAACGGT  
AATAAAAAGA AATGCCAGAA ATTTTCCCG CATTATAGGT CGACTTGCCA

4601 CTGGTTATAG GTACATTGAG CAACTGACTG AAATGCCTCA AAATGTTCTT  
GACCAATATC CATGTAATC GTTGACTGAC TTTACGGAGT TTTACAAGAA

4651 TACGATGCCA TTGGGATATA TCAACGGTGG TATATCCAGT GATTTTTTTC  
ATGCTACGGT AACCTATAT AGTTGCCACC ATATAGGTCA CTAAAAAAG

4701 TCCATTTTAG CTTCTTAGC TCCTGAAAAT CTCGATAACT CAAAAAATAC  
AGGTAAAATC GAAGGAATCG AGGACTTTTA GAGCTATTGA GTTTTTTATG

4751 GCCCGGTAGT GATCTTATTT CATTATGGTG AAAGTTGGAA CCTCACCCGA  
CGGGCCATCA CTAGAATAAA GTAATACCAC TTTCAACCTT GGAGTGGGCT

4801 CGTCTAATGT GAGTTAGCTC ACTCATTAGG CACCCCAGGC TTTACACTTT  
GCAGATTACA CTCAATCGAG TGAGTAATCC GTGGGGTCCG AAATGTGAAA

4851 ATGCTTCCGG CTCGTATGTT GTGTGGAATT GTGAGCGGAT AACAATTTCA  
TACGAAGGCC GAGCATACAA CACACCTTAA CACTCGCCTA TTGTTAAAGT

M13 Reverse primer 100.0% XbaI  
===== ~~~~~

4901 CACAGGAAAC AGCTATGACC ATGATTACGA ATTTCTAGAT AACGAGGGCA  
GTGTCCTTTG TCGATACTGG TACTAATGCT TAAAGATCTA TTGCTCCCGT

4951 AAAAATGAAA AAGACAGCTA TCGCGATTGC AGTGGCACTG GCTGGTTTTCG  
TTTTTACTTT TTCTGTCGAT AGCGCTAACG TCACCGTGAC CGACCAAAGC

EcoRV  
~~~

5001 CTACCGTAGC GCAGGCCGAT  
GATGGCATCG CGTCCGGCTA

**MS-Roche #3**  
**MS-Roche #7**  
**MS-Roche #8**

**Fig. 4a**

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Fig. 4a cont.

| Framework 3 |   |   |   |   |   |   |   |   |   | CDR 3 |   |   |   |   |   |   |   |   |   | Framework 4 |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|-------|---|---|---|---|---|---|---|---|---|-------------|---|---|---|---|---|---|---|---|---|-------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|             |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 6           |   |   |   |   |   |   |   |   |   | 9     |   |   |   |   |   |   |   |   |   | 10          |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 8           | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8     | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8           | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8     | 9 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BamHI       |   |   |   |   |   |   |   |   |   | BstI  |   |   |   |   |   |   |   |   |   | MscI        |   |   |   |   |   |   |   |   |   | BstWI |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| V           | P | A | R | F | S | G | S | G | T | D     | F | T | L | T | I | S | S | L | E | P           | E | D | F | A | V | Y | C | Q | Q | V     | Y | N | P | P | - | V | T | F | G | Q | G | T | K | V | E | I | K | R | T |
| V           | P | A | R | F | S | G | S | G | T | D     | F | T | L | T | I | S | S | L | E | P           | E | D | F | A | T | Y | C | F | Q | L     | Y | S | D | P | - | F | T | F | G | Q | G | T | K | V | E | I | K | R | T |
| V           | P | A | R | F | S | G | S | G | T | D     | F | T | L | T | I | S | S | L | E | P           | E | D | F | A | T | Y | C | Q | Q | L     | S | S | F | P | - | P | T | F | G | Q | G | T | K | V | E | I | K | R | T |

| Framework 3 |   |   |   |   |   |   |   |   |   | CDR 3 |   |   |   |   |   |   |   |   |   | Framework 4 |   |   |   |   |   |   |   |   |   |         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------|---|---|---|---|---|---|---|---|---|-------|---|---|---|---|---|---|---|---|---|-------------|---|---|---|---|---|---|---|---|---|---------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|             |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 6           |   |   |   |   |   |   |   |   |   | 9     |   |   |   |   |   |   |   |   |   | 10          |   |   |   |   |   |   |   |   |   |         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 9           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9     | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9       | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |   |   |   |   |   |   |   |   |   |   |
| BstEII      |   |   |   |   |   |   |   |   |   | NspV  |   |   |   |   |   |   |   |   |   | EagI        |   |   |   |   |   |   |   |   |   | Bst-III |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Y           | A | D | S | V | K | G | R | F | T | I     | S | R | D | N | S | K | N | T | L | Y           | L | Q | M | N | S | L | R | A | E | D       | T | A | V | Y | Y | C | A | R | R | L | T | H | Y | A | R | Y | Y | R | Y | F |
| Y           | A | D | S | V | K | G | R | F | T | I     | S | R | D | N | S | K | N | T | L | Y           | L | Q | M | N | S | L | R | A | E | D       | T | A | V | Y | Y | C | A | R | R | L | T | H | Y | A | R | Y | Y | R | Y | F |
| Y           | A | D | S | V | K | G | R | F | T | I     | S | R | D | N | S | K | N | T | L | Y           | L | Q | M | N | S | L | R | A | E | D       | T | A | V | Y | Y | C | A | R | R | L | T | H | Y | A | R | Y | Y | R | Y | F |

| Framework 3                                                                                                 |   |   |   |   |   |   |   |   |   | CDR 3 |   |   |   |   |   |   |   |   |   | Framework 4 |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|-------|---|---|---|---|---|---|---|---|---|-------------|---|---|---|---|---|---|---|---|---|------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                                                                                                             |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 6                                                                                                           |   |   |   |   |   |   |   |   |   | 9     |   |   |   |   |   |   |   |   |   | 10          |   |   |   |   |   |   |   |   |   | 11   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 9                                                                                                           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9     | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9           | 0 | a | b | c | d | e | f | g | h | i    | j | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 |
| BstEII                                                                                                      |   |   |   |   |   |   |   |   |   | EagI  |   |   |   |   |   |   |   |   |   | Bss-HII     |   |   |   |   |   |   |   |   |   | SylI |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R L T H Y A R Y Y R Y F         |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R G K G N T H K P Y G Y V R Y F |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R L L S R G Y N G Y Y H K F     |   |   |   |   |   |   |   |   |   |       |   |   |   |   |   |   |   |   |   |             |   |   |   |   |   |   |   |   |   |      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |



### Sequence of MS-Roche#3, #7 and #8

## HA

| Position    | Framework 1 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | CDR 1 |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   |       |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|-------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|---|-------|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|--|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|             | 1           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 2     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   | 3     |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|             | MseI        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | BspEI |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   | BstXI |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|             | 1           | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 0   | 1   | 2   | 3   | 4   | 5   | 6   | 7     | 8   | 9   | 0   | 1   | a   | b   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9 | 0 |       |     |     |     |     |     |     |     |     |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MS-Roche #3 | CAG         | GTG | CAA | TTG | GTG | GAA | AGC | GGC | GGC | CTG | GTG | CAA | CCG | GGC | GGC | AGC | CTG   | CGT | CTG | AGC | TGC | GGC | GCG | TCC | GGG | TTT | ACC | TTT | AGC | AGC | - | - | TAT   | GGC | ATG | AGC | TGG | GTG | GGC | CAA | GCC |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MS-Roche #7 | CAG         | GTG | CAA | TTG | GTG | GAA | AGC | GGC | GGC | CTG | GTG | CAA | CCG | GGC | GGC | AGC | CTG   | CGT | CTG | AGC | TGC | GGC | GCG | TCC | GGG | TTT | ACC | TTT | AGC | AGC | - | - | TAT   | GGC | ATG | AGC | TGG | GTG | GGC | CAA | GCC |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MS-Roche #8 | CAG         | GTG | CAA | TTG | GTG | GAA | AGC | GGC | GGC | CTG | GTG | CAA | CCG | GGC | GGC | AGC | CTG   | CGT | CTG | AGC | TGC | GGC | GCG | TCC | GGG | TTT | ACC | TTT | AGC | AGC | - | - | TAT   | GGC | ATG | AGC | TGG | GTG | GGC | CAA | GCC |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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Fig. 4b cont.

| Framework 2 |  |  |  |  |  |  |  |  |  | CDR 2 |  |  |  |  |  |  |  |  |  | Framework 3 |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  |  |  |  |  |  |   |  |  |  |  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| 7           |  |  |  |  |  |  |  |  |  | 8     |  |  |  |  |  |  |  |  |  | 9           |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  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|  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 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|  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  | 9 |  |  |  |  |  |  |  |  |  | 0 |  |  |  |  |  |  |  |  |  | 1 |  |  |  |  |  |  |  |  |  | 2 |  |  |  |  |  |  |  |  |  | 3 |  |  |  |  |  |  |  |  |  | 4 |  |  |  |  |  |  |  |  |  | 5 |  |  |  |  |  |  |  |  |  | 6 |  |  |  |  |  |  |  |  |  | 7 |  |  |  |  |  |  |  |  |  | 8 |  |  |  |  |  |  |  |  |  |

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Fig. 4b cont.

| Framework 4 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 10          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| BstXI       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 3           | 4   | 5   | 6   | 7   | 8   | 9   | 0   | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| TTT         | GCG | GTT | TAT | TAT | TGC | CAG | CAG | GTT | TAT | AAT | CCT | CCT | GTT | ACC | TTT | GGC | CAG | GGT | ACG | AAA | GTT | GAA | ATT | AAA | CST | ACG |
| TTT         | GCG | ACT | TAT | TAT | TGC | TTT | CAG | CTT | TAT | TCT | GAT | CCT | TTT | ACC | TTT | GGC | CAG | GGT | ACG | AAA | GTT | GAA | ATT | AAA | CST | ACG |
| TTT         | GCG | ACT | TAT | TAT | TGC | CAG | CAG | CTT | TCT | TCT | TTT | CCT | CCT | ACC | TTT | GGC | CAG | GGT | ACG | AAA | GTT | GAA | ATT | AAA | CST | ACG |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
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|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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Fig. 5

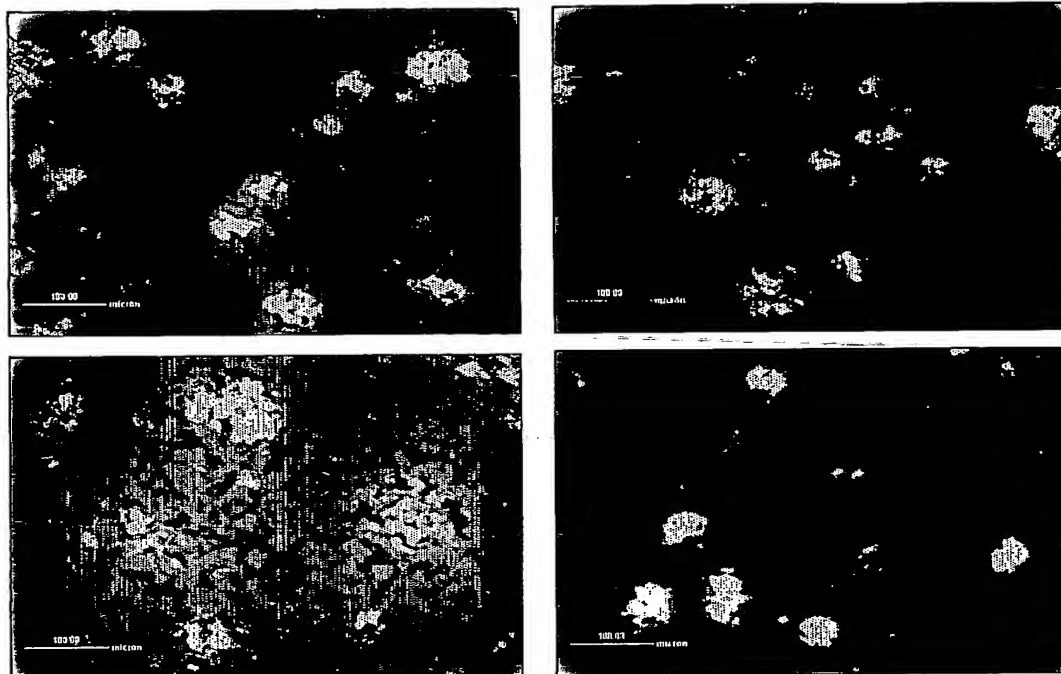
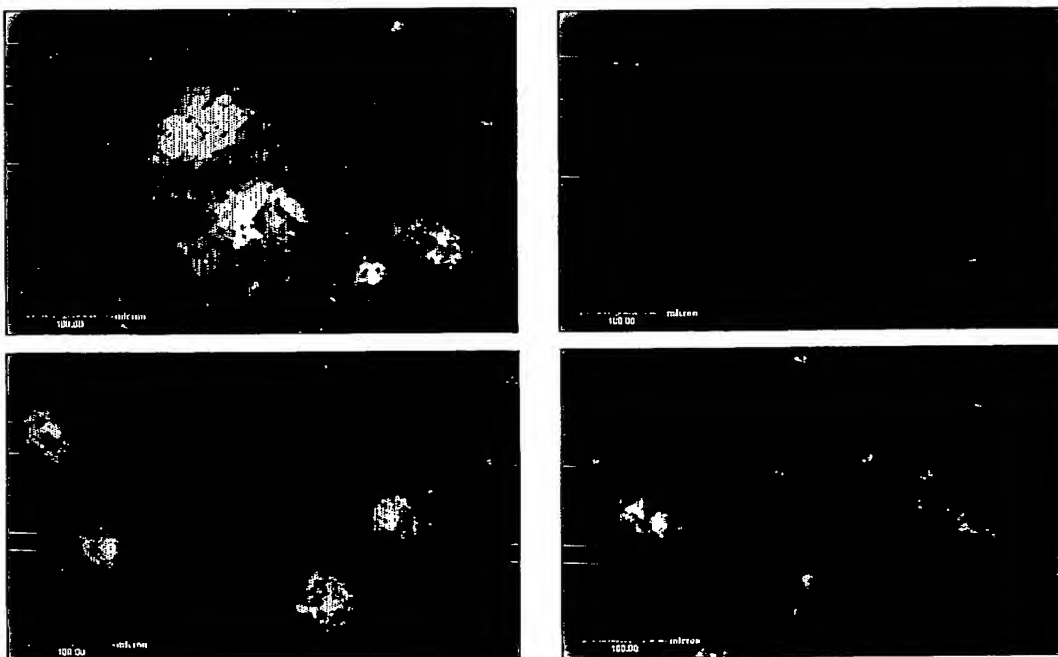


Fig. 6



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Fig. 7

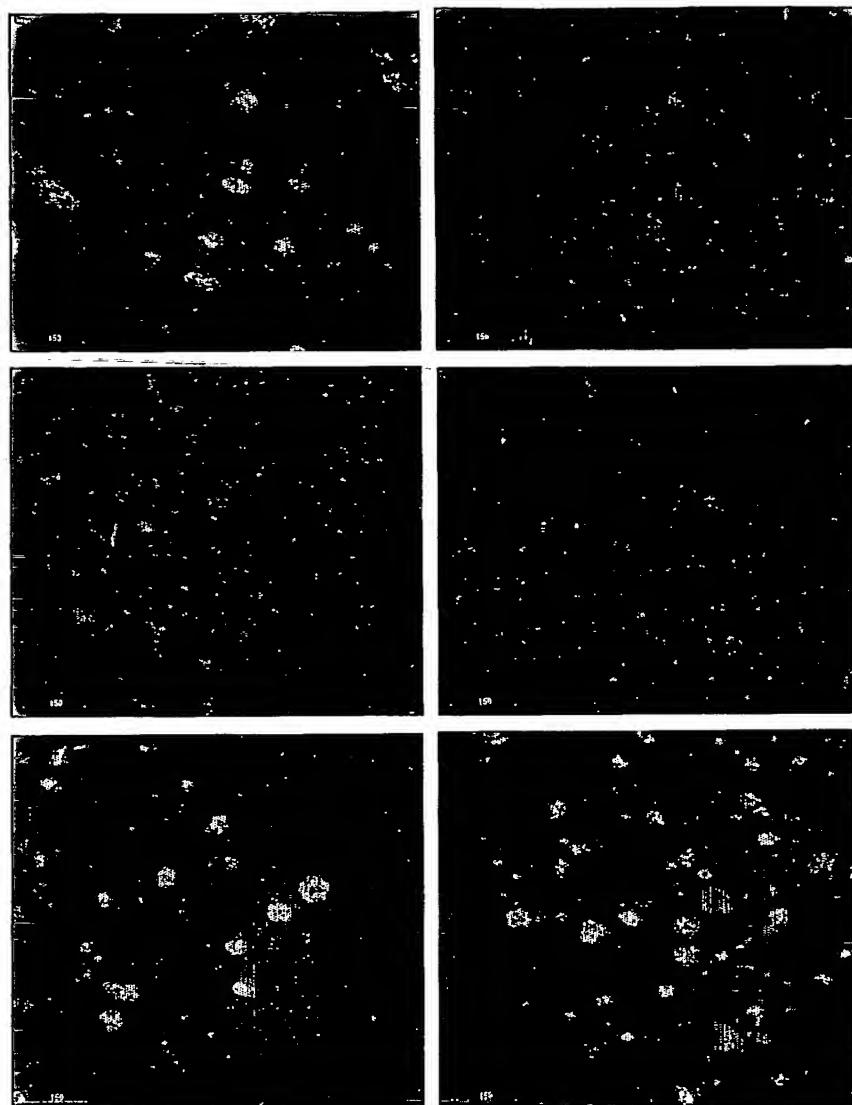
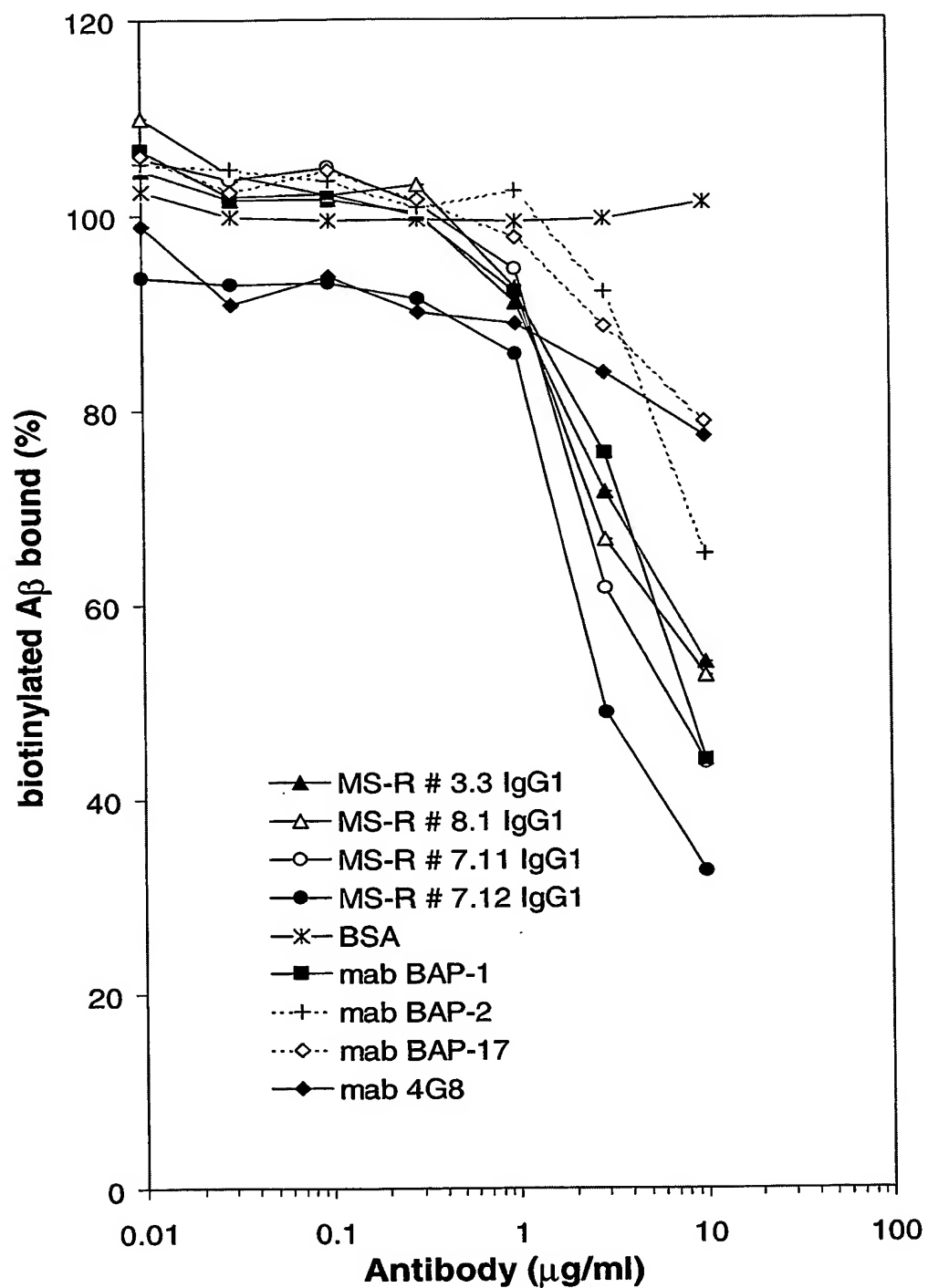
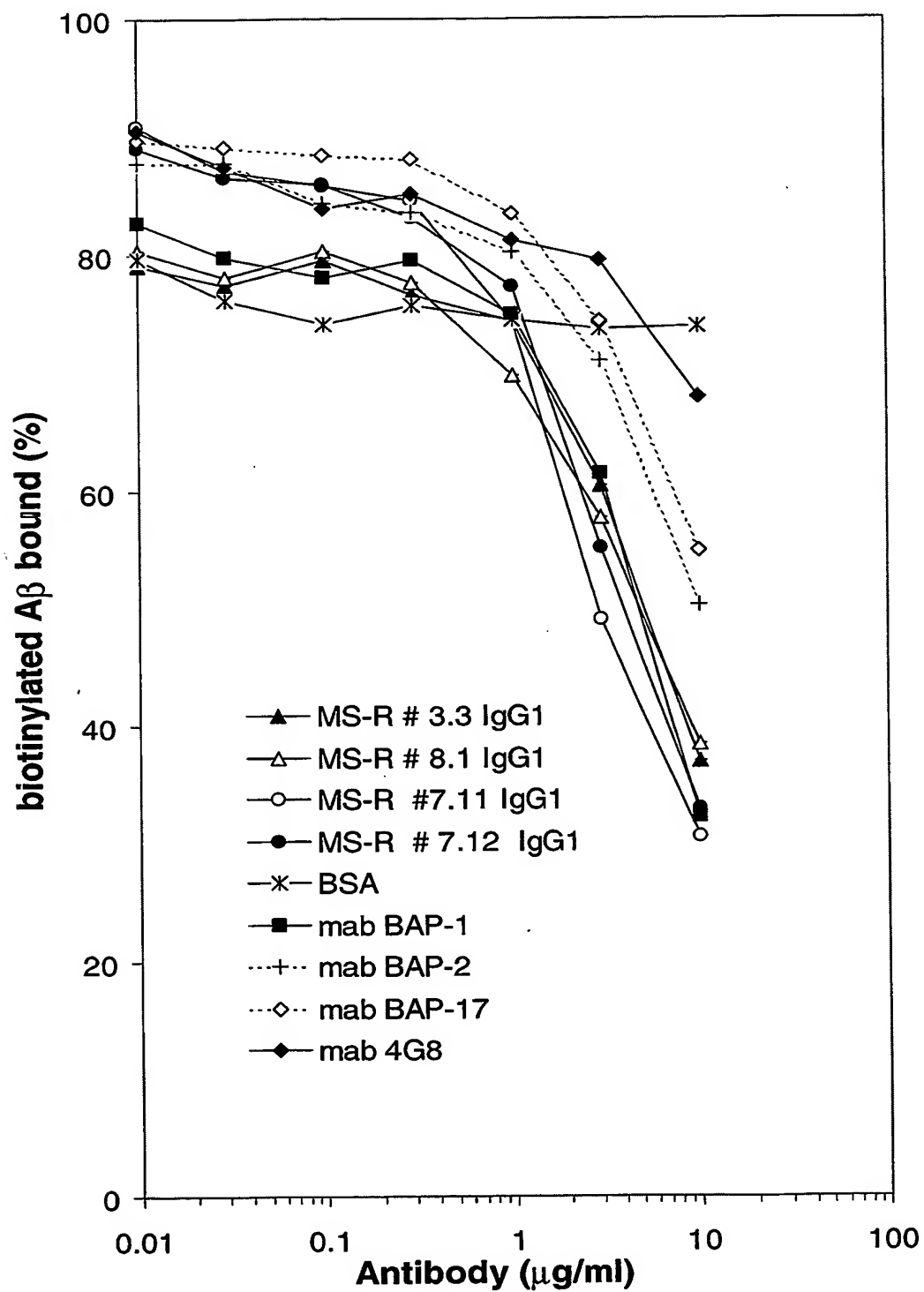


Fig. 8



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Fig. 9A

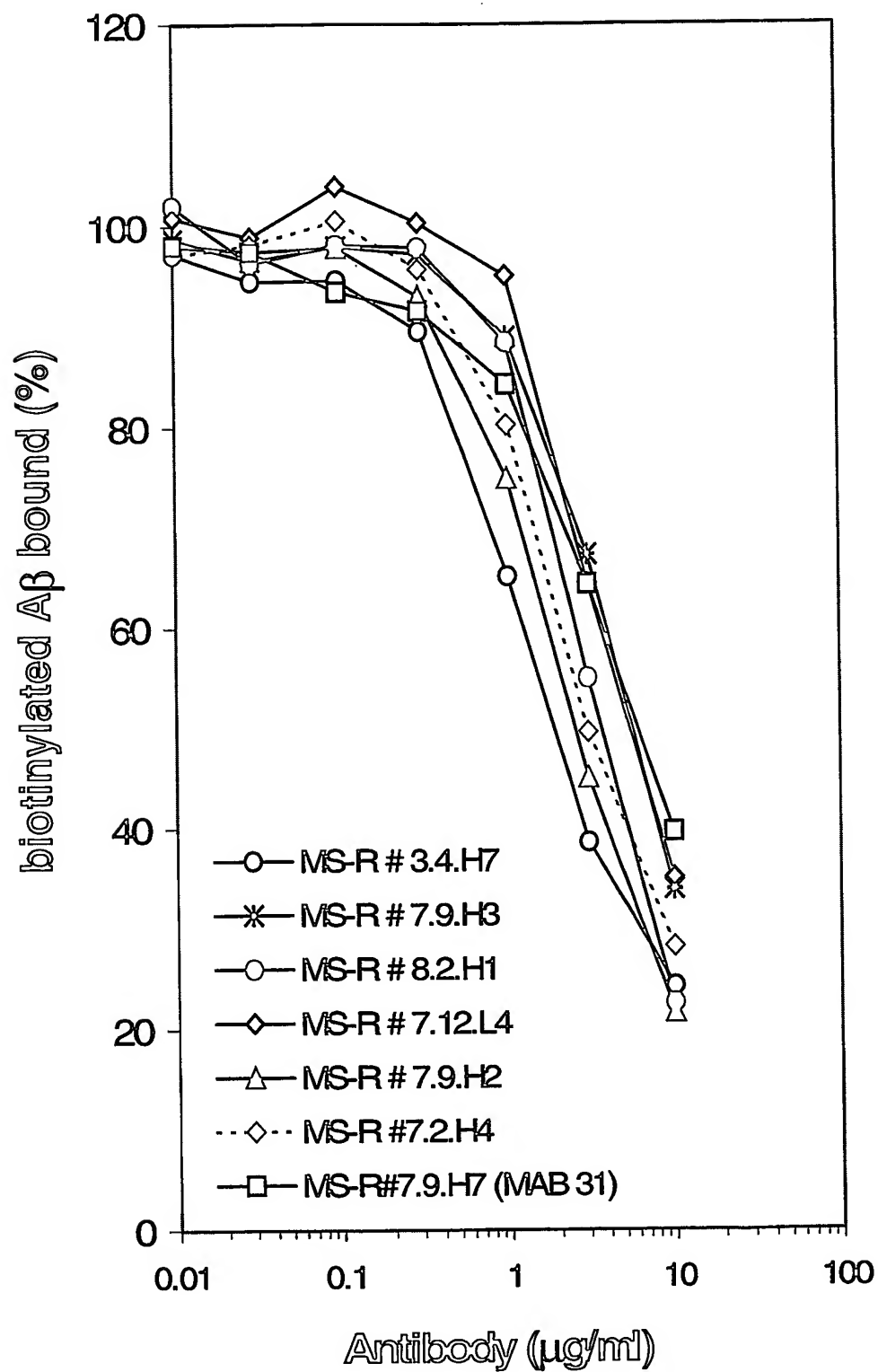
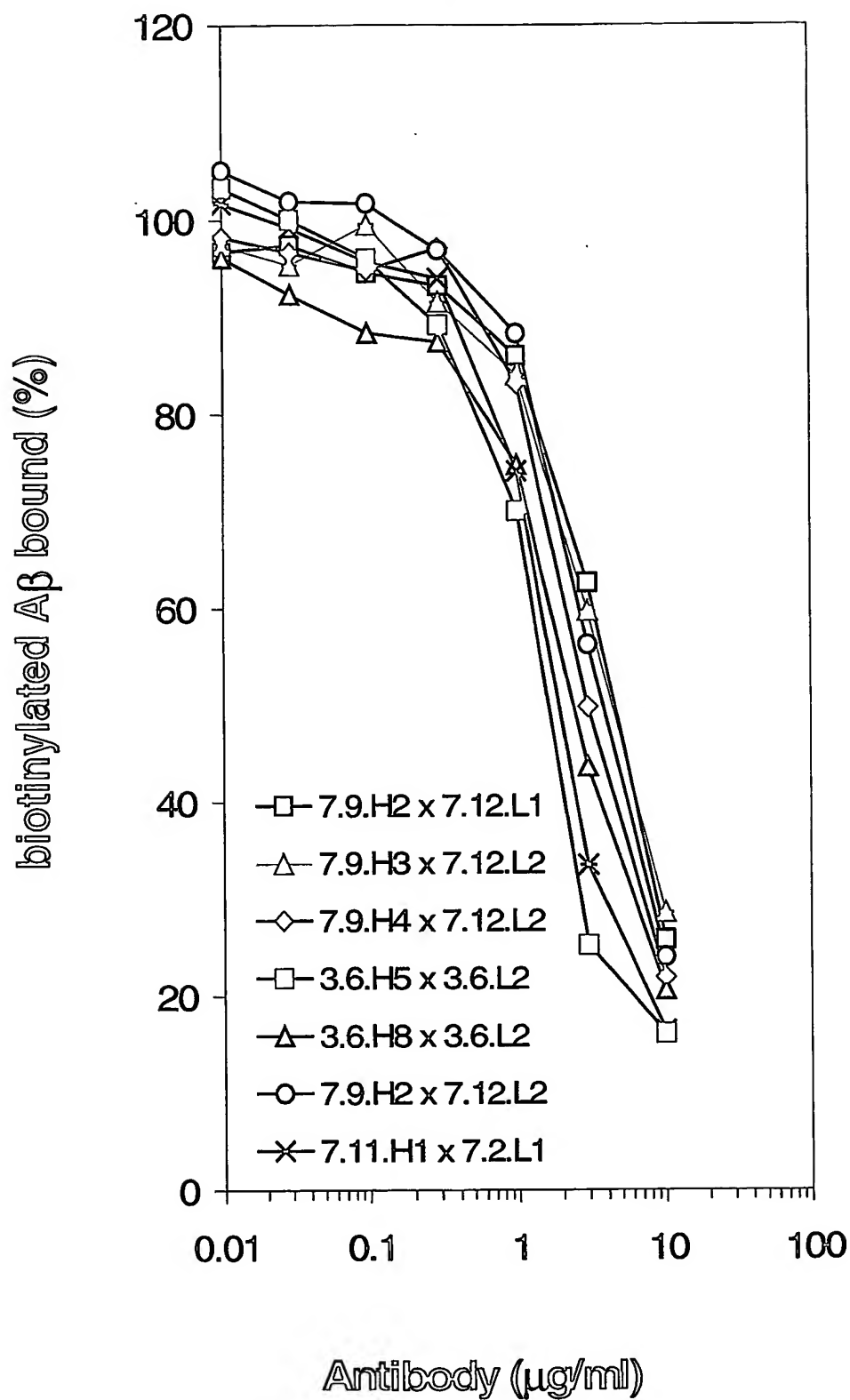
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Fig. 9B

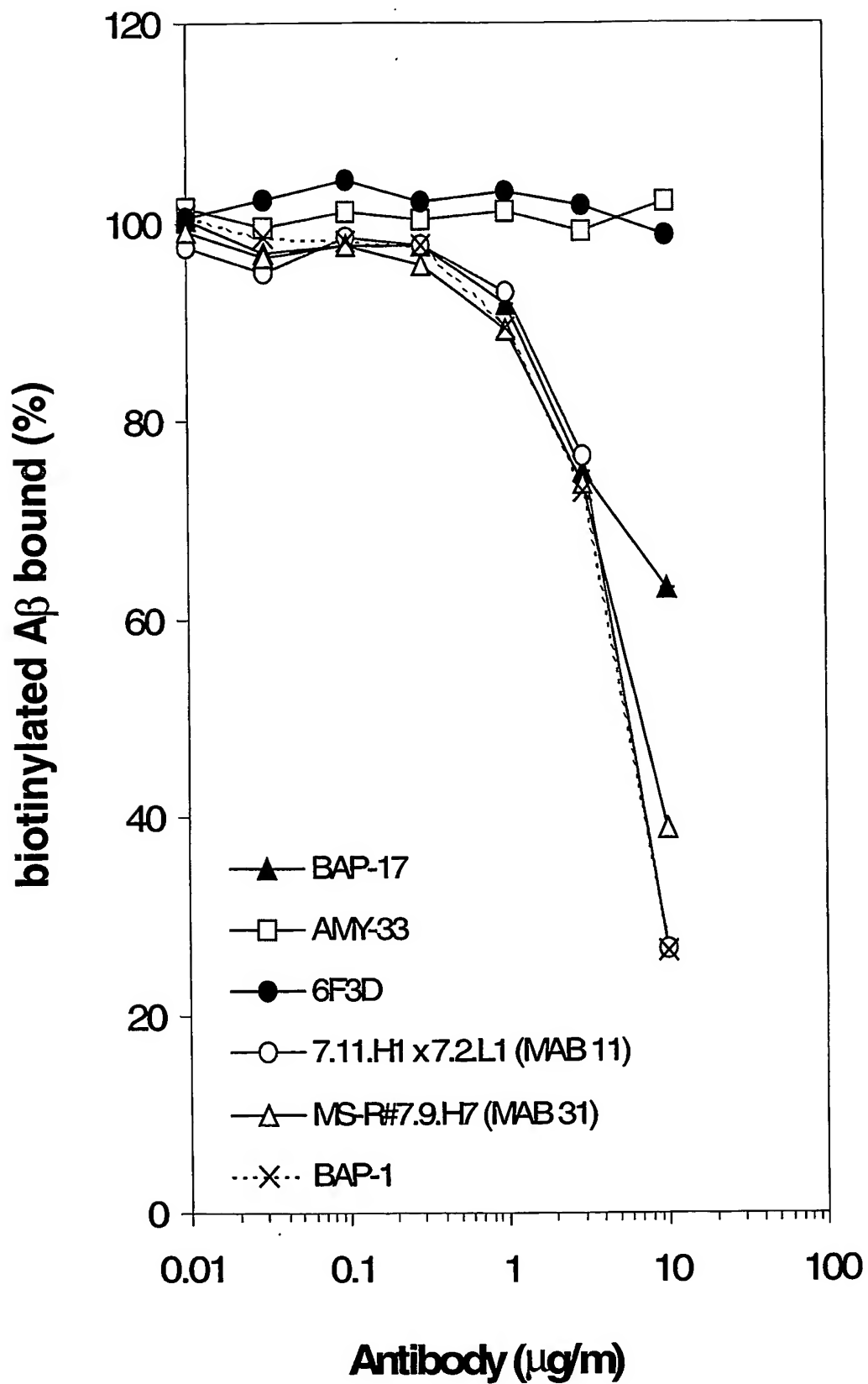


Fig. 9C



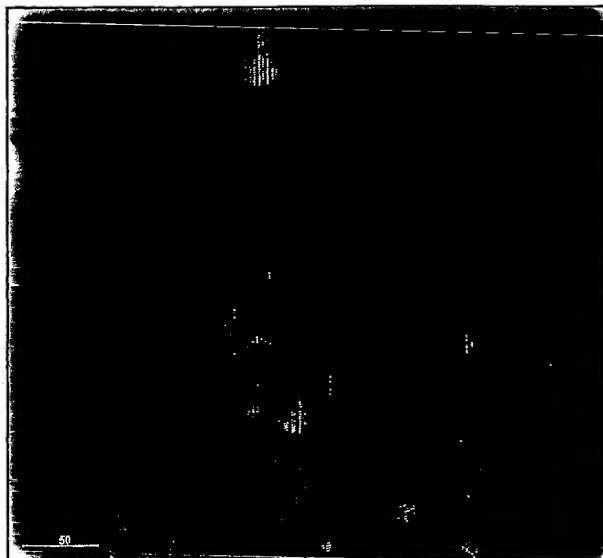
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Fig. 9D



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Fig. 10

A



B



C



D

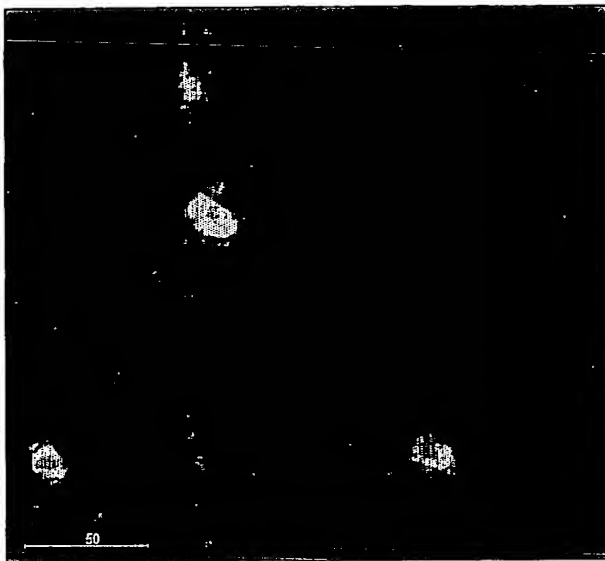


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Fig. 11

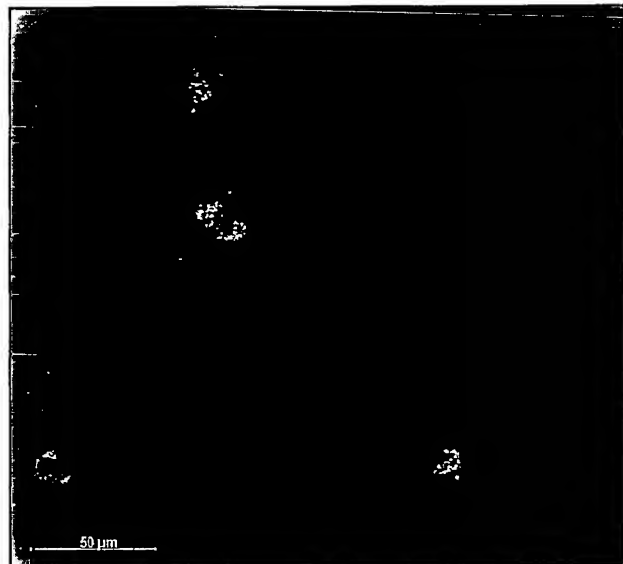
A



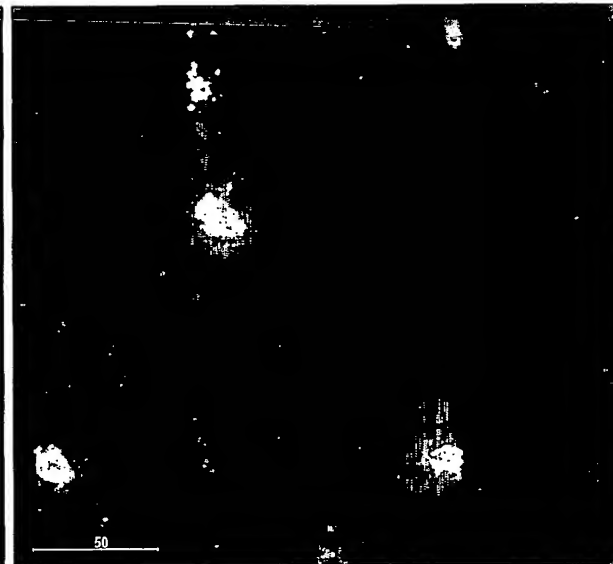
B



C

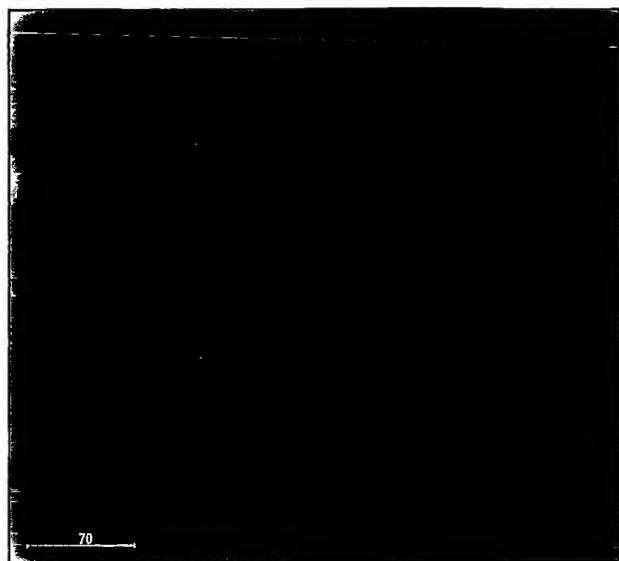


D

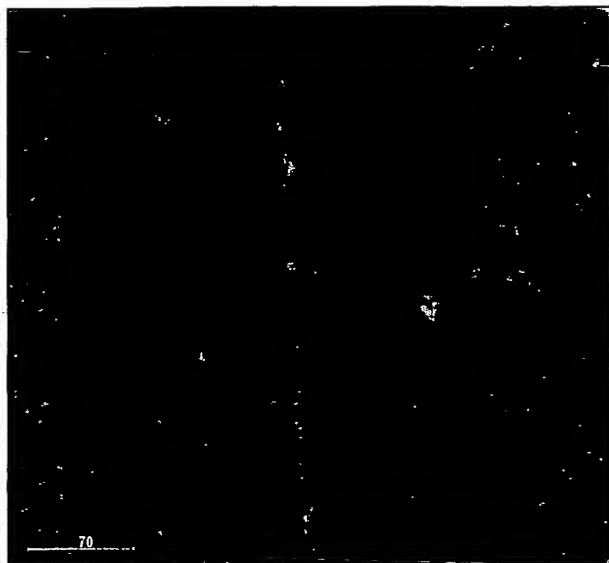


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Fig. 12

A



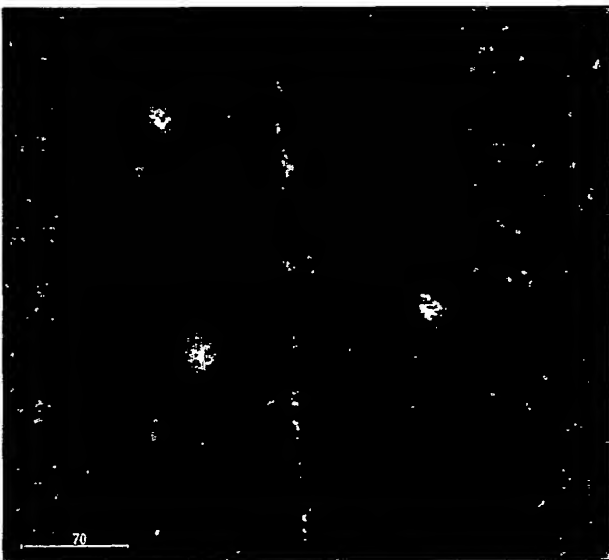
B



C

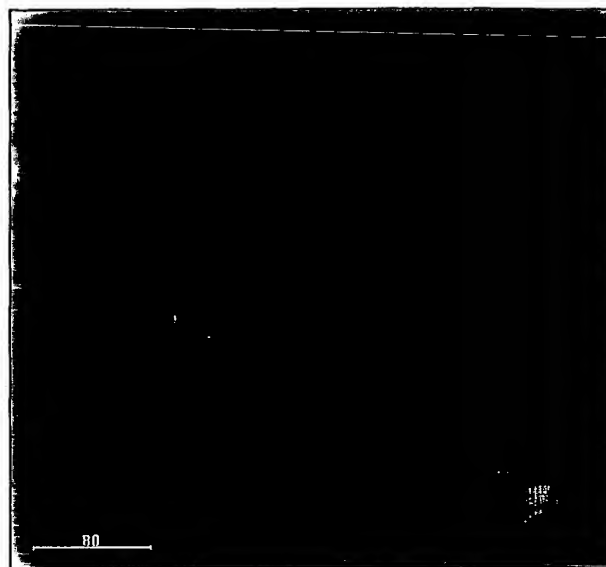


D

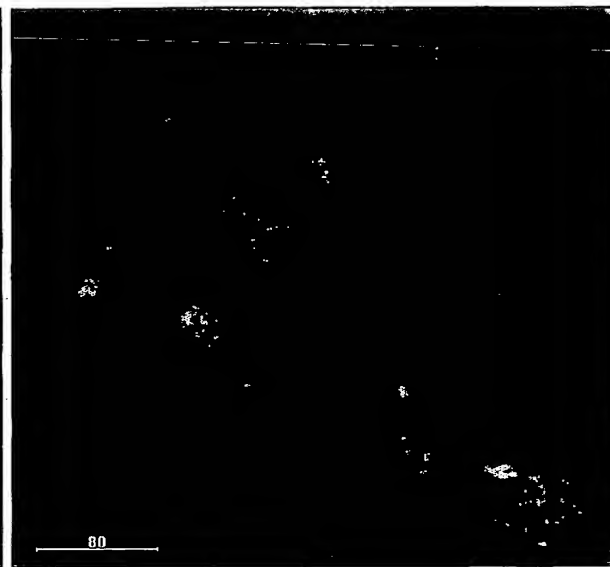


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Fig. 13

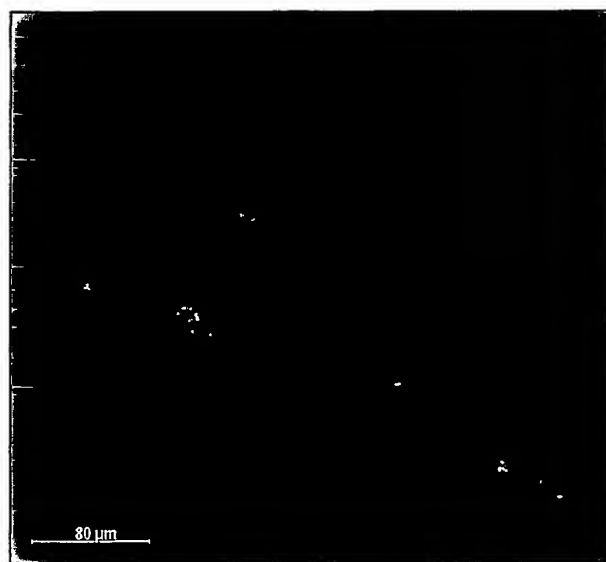
A



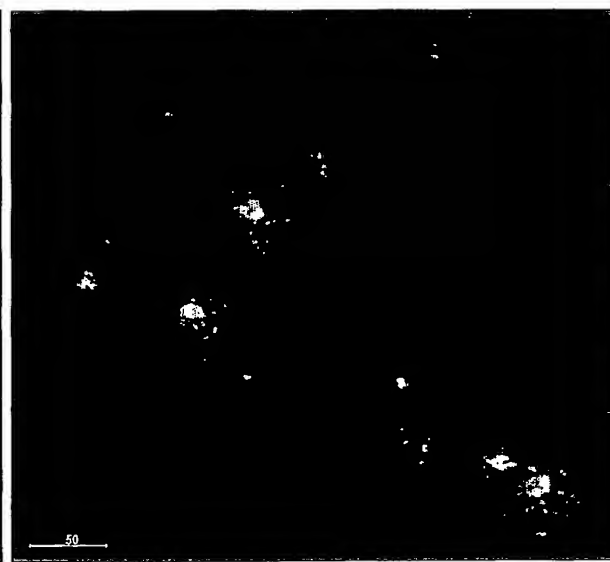
B



C

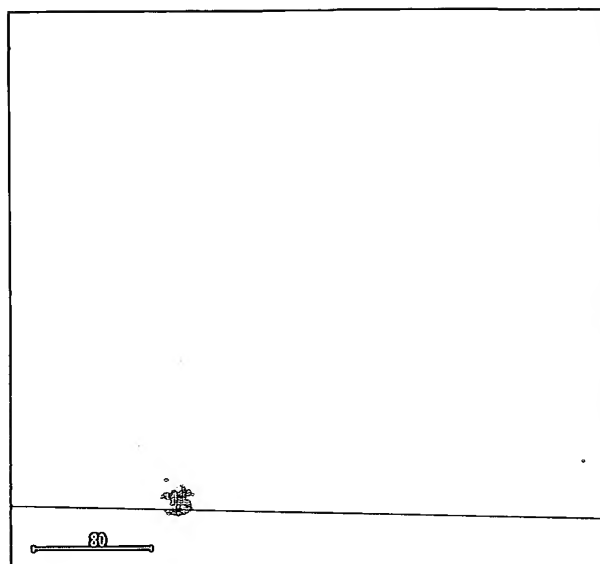


D

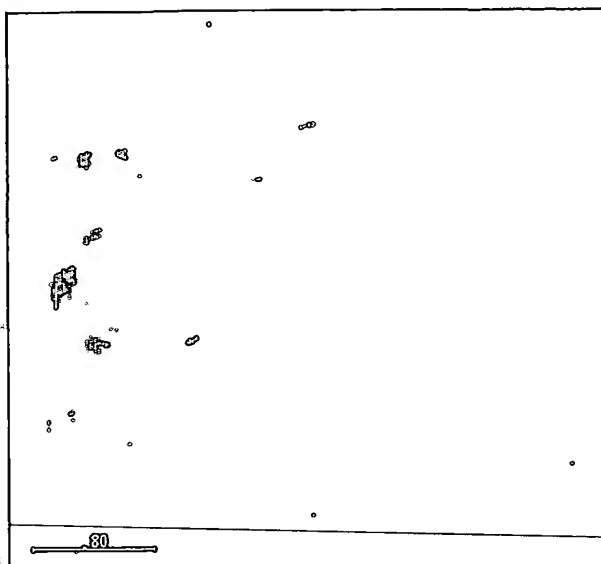


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Fig. 14

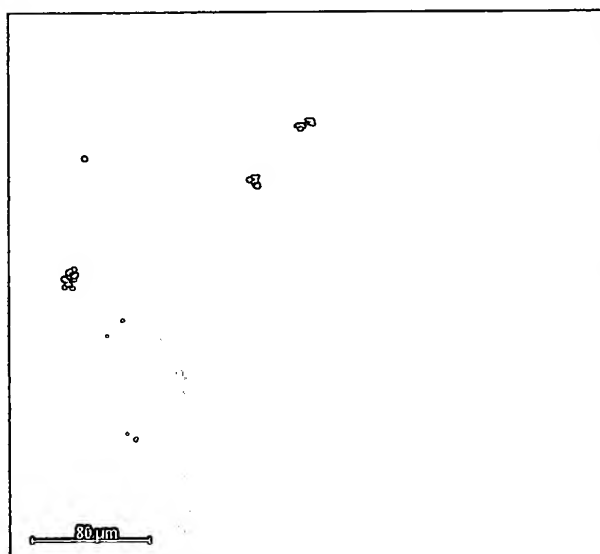
A



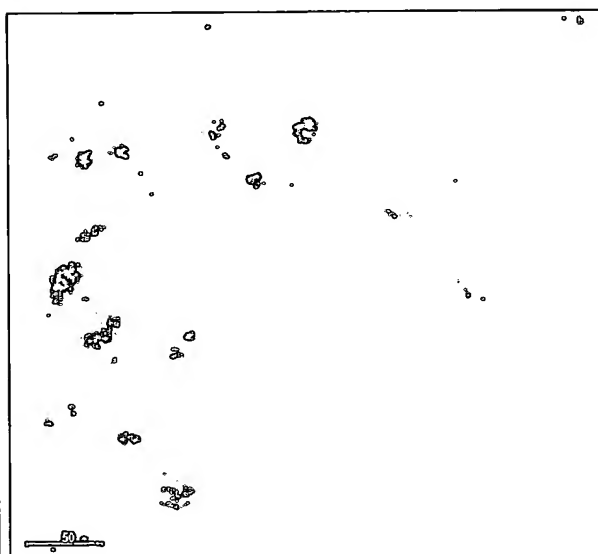
B



C

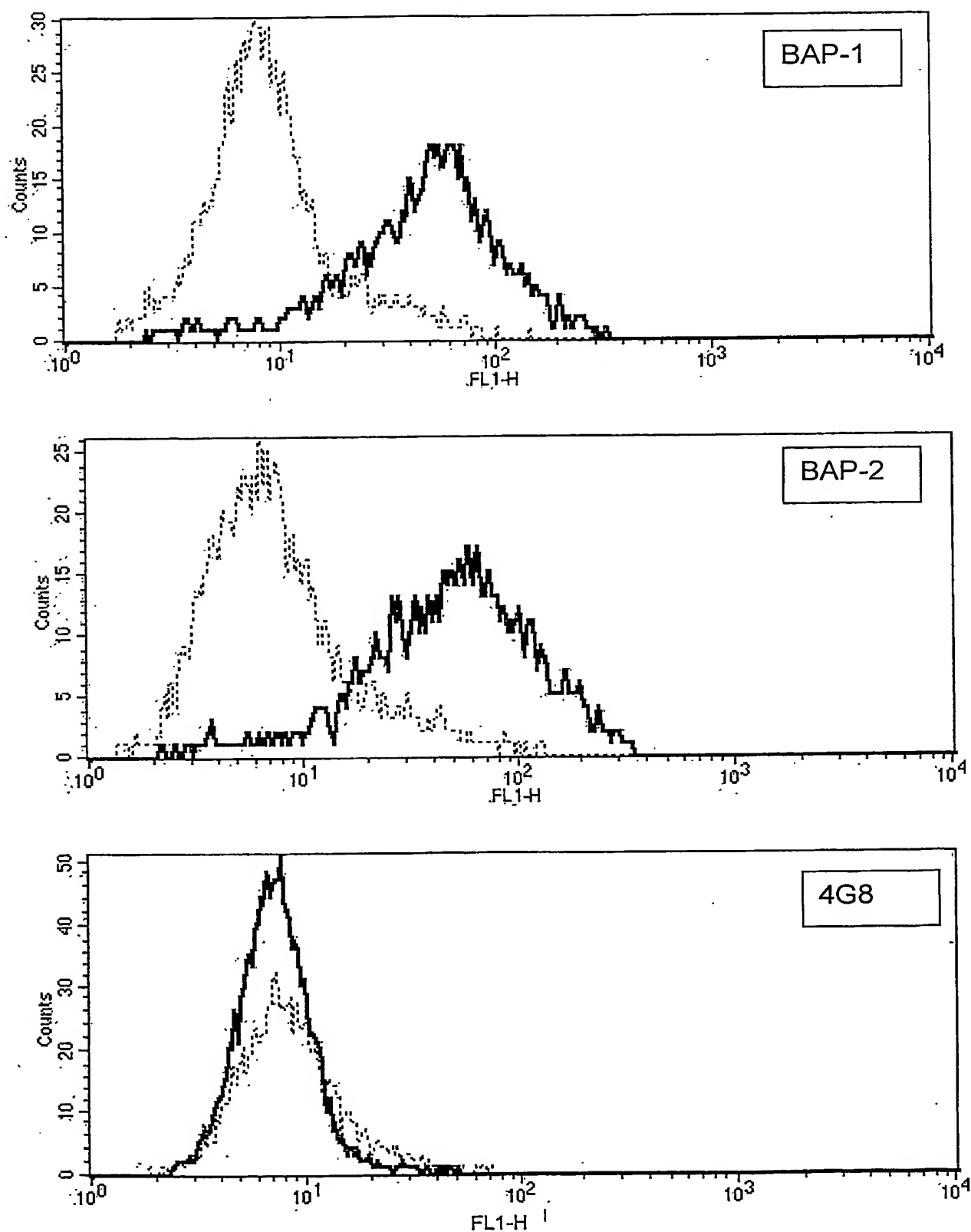


D



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Fig. 15 - 1





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Fig. 15 - 2

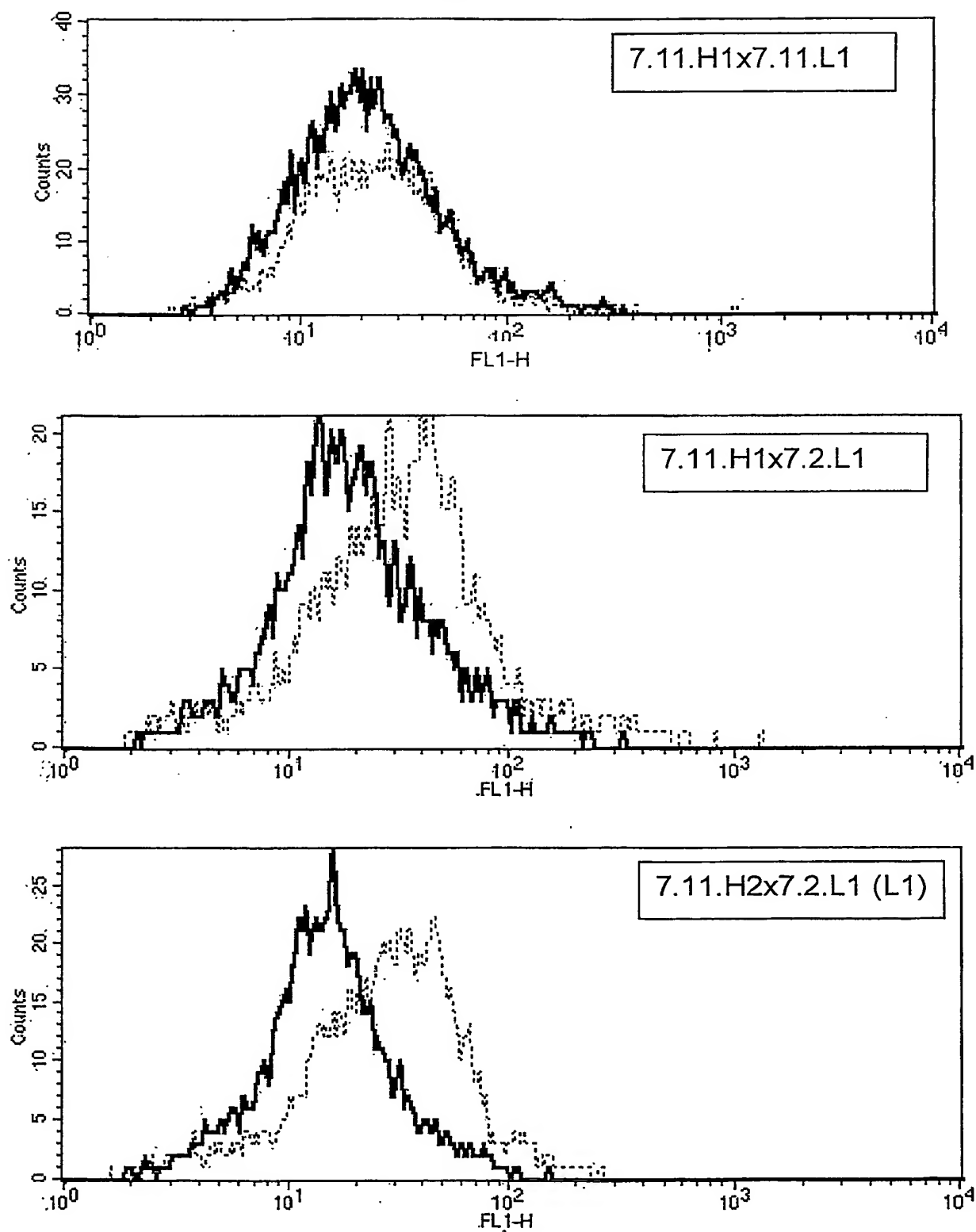


Fig. 15 - 3

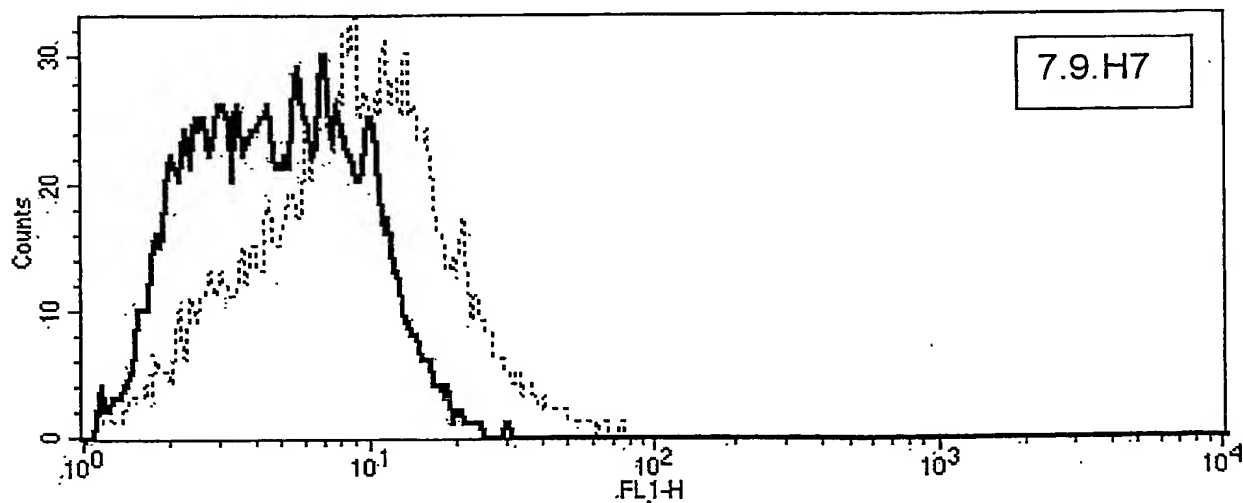
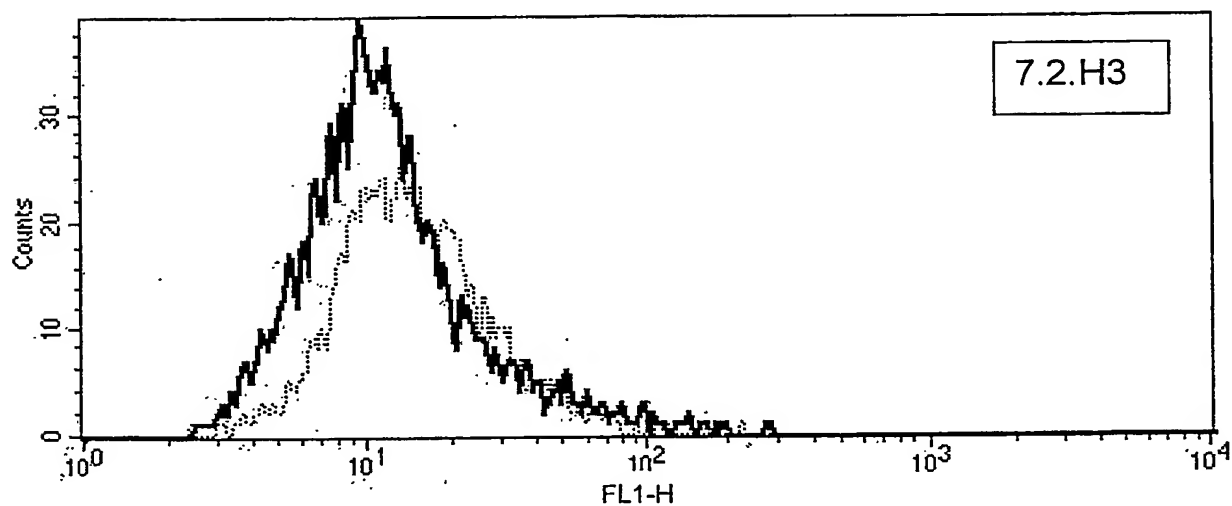
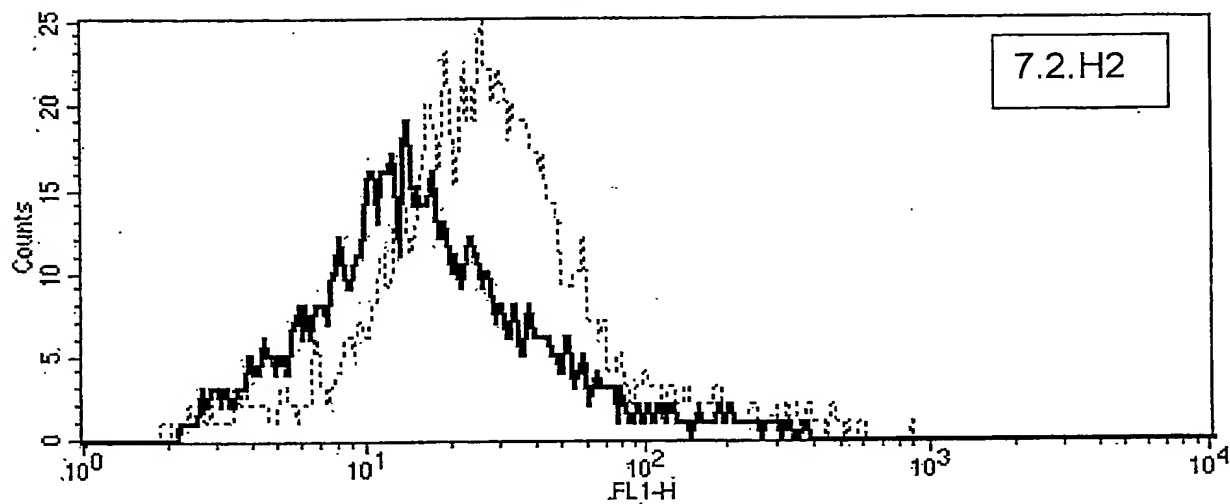
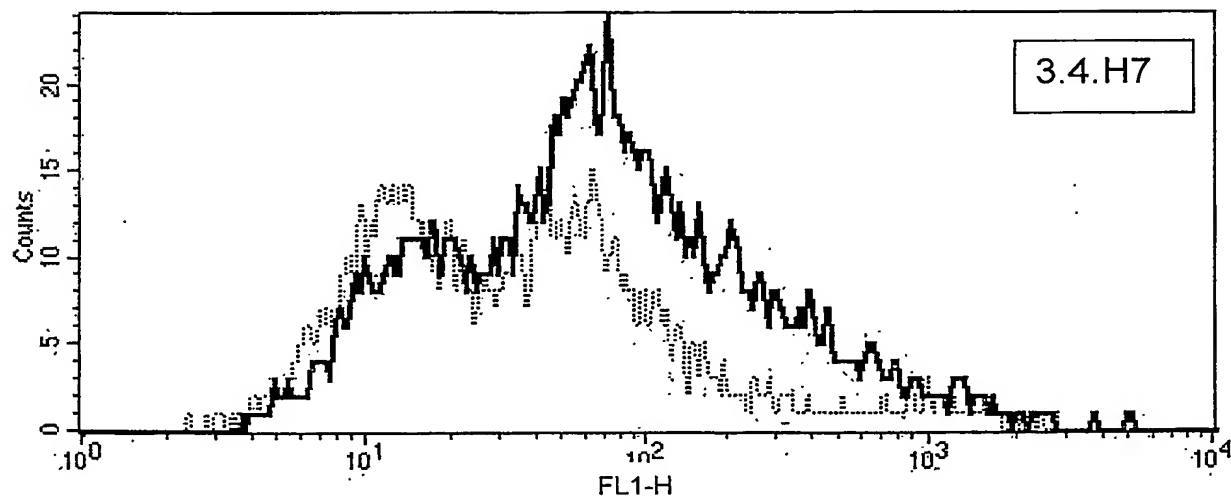
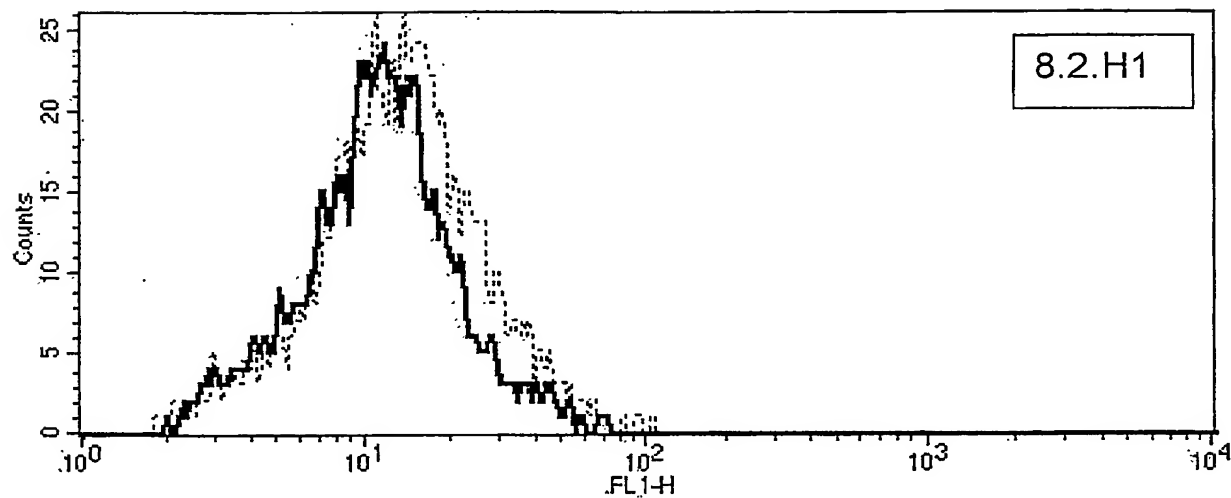


Fig. 15 - 4



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